IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMA S.A., SANOFI-AVENTIS U.S., LLC Plaintiffs, v. HOSPIRA, INC, APOTEX, INC. and APOTEX CORP., Defendants.	)	Civil Action No. 07-721-GMS (Consolidated)

DEFENDANTS' POST-TRIAL PROPOSED FINDINGS OF FACTS AND CONCLUSIONS OF LAW

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

I. Introduction

A. Introduction: Invalidity

1. On the issue of validity, Sanofi acknowledged that the alleged invention – the purported "gee whiz" – was simply swapping out one surfactant (Cremophor) for another (polysorbate 80) to formulate an old cancer compound (docetaxel). (Tr. 461:8-10 (Fabre); Tr. 636:24-637:5 (Kaler); JTX 3, '561 patent, 2:23-25.)[1] But the GV reference *expressly* disclosed that claimed invention: docetaxel in "polysorbate 80/ethanol, 1:1." (JTX 93, at 996.)

2. Before trial, the parties disputed whether GV refers to a pharmaceutical formulation (as Defendants had asserted) or merely a solution for *in vitro* cell testing (as Sanofi had asserted). At trial, Sanofi's expert, Dr. Kinam Park, *agreed* with Defendants that GV's 50/50 formulation would "destroy the cell itself" and, thus, could not be used for *in vitro* testing. (Tr. 1452:25-1463:3 (Park)). This last-minute concession proved Defendants' point: GV discloses a pharmaceutical formulation that matches up with the claimed formulation.

3. There was simply no invention here. Sanofi confirmed that swapping surfactants worked after only three days of experiments. (Tr. 454:17-455:4 (Fabre)). And the very same swap had *already* been disclosed in the prior art: first by Sandoz when formulating etoposide, then by Professor Dorr when formulating acronycine, and finally by Sanofi itself in the GV article. (Tr. 870:8-871-17 (Myrdal)). Dr. Park not only agreed with Defendants' reading of GV, but he also admitted the "Sandoz experience" with etoposide "taught Professor Dorr to switch away from Cremophor towards polysorbate 80" for acronycine. (Tr. 1501:14-17).

4. Then, in a shocking development at trial, Dr. Park effectively offered no response *at all* to Defendants' two invalidity experts. Instead, Dr. Park based his opinion on the erroneous

[1] All exhibits cited in the briefs will be separately submitted, for the Court's convenience, in electronic form this week. Defendants understand that Plaintiffs will also be separately submitting exhibits, and Defendants reserve the right to object to the exhibits if not used and ruled upon at trial.

assumption that the claims required non-existent limitations: "when [he] evaluated anticipation and obviousness, [he] believed *each claim required safety, efficacy, and stability*." (Tr. 1492:7-11 (emphasis added)). Just weeks ago, the Federal Circuit rejected a similar argument where the patentee tried to add an "effectiveness requirement" to claims that, like here, did not include "any specific dosage or amount, or even an 'effective amount.'" *Iovate Health Scis. v. Bio-Engineered Supplements*, 2009 WL 3855928, at *4 (Fed. Cir. Nov. 19, 2009).

B. Introduction: Inequitable Conduct

5. The asserted patents are also unenforceable for inequitable conduct. Named inventor Mr. Fabre ultimately conceded his "main references" in making the claimed invention were "the taxol formulations and the Sandoz formulations." (Tr. 477:1-478:5 (Fabre)). An internal development memo confirmed the same thing. (JTX 162, at 1). Despite this, Sanofi's inventors never disclosed to the Patent Office the Sandoz prior art, published in the Vidal. (Tr. 478:10-23 (Fabre)).

6. Additionally, Mr. Fabre knew about but did not disclose the GV reference. He knew that it was relevant to the prosecution of the patents-in-suit because he insisted that it be cited in an Investigators' Brochure for physicians conducting clinical trials on the drugs months before he signed a declaration for the application for the '561 Patent. (Tr. 472:12-474:2 (Fabre)).

7. Sanofi tried to justify its concealment by arguing that its efforts to make Sandoz's "etoposide-type" formulations had failed. First, no amount of *confidential* experimentation can justify concealing *published prior art*, particularly not the very art the inventors copied for their claimed invention. Second, Sanofi's experiments did not fail. Sanofi made *several* successful "etoposide-type" formulations. (Tr. 442:12-443:24; 449:20-452:1 (Fabre)). Sanofi's deceptive intent is shown by the materiality of these items and a pattern of other misrepresentations.

C. Introduction: Non-Infringement (Hospira)

8. Hospira does not infringe the asserted claims. For starters, Hospira's lead formulator Julie Liu created a much better product using only one vial (instead of Sanofi's two), which is more convenient (no premix and multi-dose use) and more stable (two years instead of Sanofi's eight hours for a premix). (Tr. 740:8-16, 741:9-742:17, 744:19).

9. Hospira's improved formulation does not infringe claims 2 and 10 of the '561 patent, which require a formulation "consisting essentially of" only two inactive ingredients – ethanol and polysorbate 80. Hospira adds two extra ingredients, citric acid and PEG 300 (Tr. 774:12-21 (Liu)), and experiments proved that without them, the product would have failed as it would fall apart almost immediately. (Tr. 759:3-760:15 (Liu); JTX 107, at 5). Sanofi effectively admitted the ingredients impact the basic and novel properties of the claimed invention. Sanofi later added citric acid to its own product to create a "more physically and chemically stable formulation of docetaxel." (HTX 345, at S-19). Moreover, Mr. Fabre, conceded that "including PEG in a formulation makes it different" than the claimed invention. (Tr. 450:8-22 (Fabre)).

10. Hospira also does not infringe any of the three asserted claims of the '561 patent because they require a "reasonable expectation of being injected without … anaphylactic or alcohol intoxication manifestations." (D.I. 347, Claim Constr. at 3). Far from having a reasonable expectation of *avoiding* anaphylactic manifestations, Hospira's product (just like Taxotere) will positively *cause* anaphylactic manifestations, particularly considering the thousands of patients that will use the product.

11. Finally, Hospira does not infringe claim 7 of the '512 patent, which requires a product that is "essentially free of ethanol." An ethanol-free formulation will not even work, as Sanofi determined when its 2% ethanol formulation required an "extraordinarily cumbersome" 13-step administration procedure that ultimately forced it to add 12% ethanol back to its product.

(Tr. 487:10-489:4 (Fabre)). Hospira's stock solution, too, is not "essentially free of ethanol" as it has 23% ethanol while the claim requires less than 5% ethanol. Hospira's perfusion also falls outside any sensible reading of this Court's claim construction for a perfusion: "the same amount of ethanol as a stock solution with no more than 5% ethanol by volume." (D.I. 347, at ¶ A.2). Hospira's perfusion has the "same amount" of ethanol as its *non-infringing 23%* stock solution, so it cannot infringe.

D. Introduction: Non-Infringement (Apotex)

12. Apotex does not infringe the asserted claims. Sanofi does not even allege that Apotex's concentrate or diluent infringe, since they must be combined by someone other than Apotex to prepare an allegedly infringing formulation. (D.I. 315 Pre-Trial Order ("PTO") Appx. B-2 ¶ I.B.2.c-d). In alleging this indirect infringement, however, Sanofi failed to prove that Defendants have a specific intent to induce infringement or, as to contributory infringement, knowledge that their NDA products are especially made or adapted to infringe.

13. Claims 2 and 10 of the '561 Patent do not read on the premix or a perfusion made from Apotex's NDA product. First, like Hospira's NDA product, Apotex's NDA product includes PEG 300, which affects the basic and novel properties. (ATX 552.0514; Tr. 1151:6-7 (Williams); ADX.1-3). Second, claims 2 and 10 require that docetaxel is "dissolved in a mixture of ethanol and polysorbate." (JTX 3). However, in Apotex's NDA product, docetaxel is dissolved in PEG 300, not polysorbate, and docetaxel remains "dissolved" in PEG 300 in the premix and a perfusion. (ATX 552.0514; Tr. 1151:6-7 (Williams); ADX.1-3).

14. Claims 2, 5, and 10 of the '561 Patent do not read on the premix or a perfusion made from the Apotex NDA product for the same reasons as Hospira's product and Taxotere: they do not avoid "anaphylactic manifestations."

15. Claim 7 of the '512 patent does not read on Apotex's injection concentrate because the injection concentrate does not contain polysorbate, a required limitation. (PTO Appx. A ¶ 61; ATX 552.0412, 0482, 0514; Tr. (Williams) at 1141:3-1142:1; ADX.1-9). Further, a perfusion made from Apotex's NDA product does not meet the "essentially free or free of ethanol" limitation of claim 7. Even assuming that Apotex's premix is a stock solution – a contention Sanofi maintains notwithstanding its concession that the premix is an intermediate dilution and not a "concentrated solution" (PTO Appx. A ¶ 60) — the premix contains 6.3% ethanol by volume, greater than the claim's requirement of 5% ethanol.

16. Lastly, Apotex does not infringe claim 33 of the '512 Patent. Sanofi alleges that claim 33 reads on Apotex's premix, but it is undisputed that the premix is an intermediate dilution and not a "concentrated solution" as required by the claim. (PTO Appx. A ¶ 60). Further, claim 33 does not read on the premix because the docetaxel in Apotex's injection concentrate is "dissolved" in PEG 300 and not polysorbate.

II. The Asserted Claims Are Anticipated And Obvious.

A. Proposed Findings Of Fact On Anticipation And Obviousness

1. The Claimed Invention Is A Drug Formulation, Not A New Drug.

17. Throughout the trial, beginning with opening statements, Sanofi confused the subject matter of the asserted patents, U.S. Patent Nos. 5,714,512 and 5,750,561. Contrary to Sanofi's suggestion, the asserted patents do *not* relate to a new cancer drug nor a medical use, but only to a *composition* for an *old* cancer drug, docetaxel. (Tr. 438:5-10 (Fabre)).

18. Sanofi's U.S. Patent No. 4,814,470 – prior art issued in 1989 – already claimed docetaxel itself and, in fact, also claimed docetaxel in a pharmaceutical formulation. (JTX 9, at 10:13-45). In the example disclosed in the '470 patent, docetaxel was formulated in ethanol and

Cremophor (called Emulphor) (JTX 9, at 10:5-11), though the specification made clear there was "a wide range of different formulations you could use." (Tr. 837:9-15 (Myrdal)).

19. For its purported invention – which it came up with and confirmed worked after only *three* days of experiments (Tr. 454:17-455:4 (Fabre)) – Sanofi simply replaced Cremophor with polysorbate 80: "The present invention then makes it possible to replace the Cremophor, described in the publication of the Journal of National Cancer Institute, by a polysorbate." (JTX 3; '561 patent at 2:23-30). The inventor Mr. Fabre also acknowledged that his "claimed invention was to swap out Cremophor for polysorbate 80." (Tr. 461:8-10 (Fabre)).

2. The GV Reference Expressly Disclosed The Claimed Formulation.

20. In the GV article, Sanofi expressly disclosed the swap that Sanofi now claims as its alleged invention: "taxotere showed a better solubility in excipient system (***polysorbate 80***/ethanol, 1:1)." (JTX 309, at 996; Tr. 841:9-842:14 (Myrdal), 471:11-21 (Fabre)). At trial, Mr. Fabre admitted that GV disclosed the very same "1:1" formulation that Sanofi first brought to clinical trials in June 1990 – a 50/50 formulation of ethanol and polysorbate 80. (Tr. 471:18-24 (Fabre)). That was nine months before Sanofi published the formulation in GV. (JTX 309, at 1; Tr. 469:21-470:6 (Fabre)).

21. In response to all of this, Sanofi's main argument had been that GV was only disclosing a solution for *in vitro* tests rather than a clinical pharmaceutical formulation. First, even if that *were* true (which it is not), that would not change the fact that GV still disclosed a "stock solution" of docetaxel under the claims, which means only a "concentrated solution." (Tr. 1174:5-1175:2 (Williams); D.I. 347, at ¶ A.1).

22. Moreover, there is no question that GV in fact discloses a pharmaceutical formulation rather than an *in vitro* solution. GV used the phrase "excipient system," which is clearly "a pharmaceutical system, especially in the context of this right here." (Tr. 841:9-21

(Myrdal)). GV also reported a "better solubility" of docetaxel in the polysorbate 80 formulation – relevant to pharmaceutical formulations, not to *in vitro* solutions. (Tr. 842:7-24 (Myrdal)).

23. Dr. Williams described as "absurd" Sanofi's argument that GV merely disclosed an *in vitro* solution. (Tr. 1191:14-1192:5 (Williams)). He explained that 50% ethanol "is toxic to cells in *in vitro* testing" and 50% polysorbate "is a cell membrane disrupting molecule, and that's also toxic." (*Id.*) Instead of attempting to rebut this testimony, Sanofi's expert, Dr. Park, ***agreed*** that the GV 50-50 formulation could ***not*** have been used for *in vitro* tests because it would kill the cells: "if you add the more than .1 percent polysorbate, you will destroy the cell itself." (Tr. 1462:25-1463:3 (Park)). Thus, in the end, Sanofi offered no rebuttal to the plain fact that GV expressly disclosed the claimed formulation using polysorbate 80 instead of Cremophor.

3. Sanofi's Allegedly New Formulation Followed A Standard Surfactant/Ethanol Model For Insoluble Cancer Compounds.

24. In addition to having been expressly disclosed in GV, Sanofi's supposedly new pharmaceutical formulation merely copied a standard approach for cancer compounds that, like docetaxel, were insoluble in water. That standard approach was to combine ethanol with a surfactant, a common ingredient that helps dissolve poorly water soluble drugs. (Tr. 869:12-871:6 (Myrdal)). A surfactant helps the cancer compound stay in solution. (*See* Tr, 1228:12-1229:1 (Williams); HTX 281, at 2 n.2; HTX 373, at No. 7).

4. There Were Only Two Established Surfactant Choices: Cremophor and Polysorbate 80.

25. By the priority date in July 1991, the ethanol/surfactant approach was completely conventional for formulating cancer compounds (Tr. 836:21-837:3 (Myrdal)), using only one of two surfactants—Cremophor or polysorbate 80:

Prior Art		Drug	Ethanol	Surfactant
GV Article	(JTX 93)	Docetaxel	Yes	Polysorbate 80
'470 patent	(JTX 9)	Docetaxel	Yes	Cremophor (Emulphor)
Rowinsky	(JTX 15)	Paclitaxel	Yes	Cremophor
Miller	(JTX 135)	Paclitaxel	Yes	Polysorbate 80
Miller	(JTX 135)	Cephalomannine	Yes	Polysorbate 80
Vidal	(JTX 101)	Etoposide	Yes	Polysorbate 80
Vidal	(JTX 101)	Teniposide	Yes	Cremophor
Dorr	(JTX 215)	Acronycine	Yes	Polysorbate 80
Tarr	(JTX 16)	Paclitaxel	Yes	Polysorbate 80

26. Dr. Myrdal's exhaustive investigation confirmed Cremophor and polysorbate 80 were the only two surfactants used in FDA-approved injectable drugs by 1991. (Tr. 842:25-843:12, 844:16-846:17 (Myrdal)). That still remains true, as "over the last 20 years…these really have been the only two choices." (Tr. 848:19-849:5 (Myrdal)). Sanofi failed to identify any other surfactant *ever* used in an FDA-approved injectable product. (Tr. 1497:20-24 (Park)).

5. Polysorbate 80 Was The Only Reasonable Choice.

27. Between the two options for a surfactant, the obvious choice for docetaxel was polysorbate 80, tested and confirmed to work after only *three days*. (Tr. 454:17-455:4 (Fabre)).

28. Multiple prior art references identified Cremophor as a likely cause of anaphylactic manifestations. (JTX 101 (Vidal) at Hospira 155161; JTX 215 (Dorr) at 32; JTX 102 (O'Dwyer) at 960). Inventor Fabre admitted that the prior art already provided a solution to that problem, and that the prior art provided a "reasonable expectation" that "using polysorbate rather than Cremophor would avoid anaphylactic manifestations." (Tr. 468:4-13 (Fabre)).

29. Dr. Williams similarly explained that "[i]t was routine at that time to swap basically the two choices for surfactant at the time, which were Cremophor and polysorbate, one for the other." (Tr. 1187:11-19 (Williams)). Sanofi's Dr. Park failed to challenge this conclusion during discovery, stating "honestly, I don't know," and ultimately conceded at trial that the prior art taught the swap. (Tr. 1498:10-1499:3, 1501:14-17 (Park)).

30. Dr. Myrdal similarly explained that, by 1991, the advantage of using polysorbate 80 instead of Cremophor was apparent from even the most basic reference books, including the 1986 Handbook of Pharmaceutical Excipients. The Handbook provides "two columns" of safety precautions for Cremophor, including a specific warning that it is "associated with anaphylactic reactions." (Tr. 851:15-852:1 (Myrdal); JTX 91, at 222-223). By contrast, it had a single sentence about polysorbate 80, saying it is "well tolerated, practically non-irritating, very low toxicity." (Tr. 852:25-853:3 (Myrdal); JTX 91, at 227). The choice was obvious: "If I have a choice of two things, I am going to go towards the one that is safer." (Tr. 853:9-19 (Myrdal)).

31. In fact, multiple prior art references – none of which were disclosed to the Patent Office – specifically taught the benefit of swapping Cremophor for polysorbate 80, including the Vidal, Dorr, and O'Dwyer Dorr references. (JTX 101; JTX 215; JTX 102).

6. The "Vidal" Alone Made Obvious The Swap To Polysorbate 80.

32. The 1989 "Dictionnaire Vidal" (the French equivalent of the Physicians' Desk Reference) described Sandoz's experience with two related cancer compounds – the earlier-developed teniposide (with Cremophor) and the later-developed etoposide (with polysorbate). (JTX 101, at 1-4; Tr. 864:8-19 (Myrdal)).

33. For teniposide, the Vidal called out Cremophor as the culprit for possible severe side effects: "This medication contains Cremophor EL as an excipient, which is likely to lead to anaphylactogenic reactions" – a danger that required requires "a source of oxygen . . . available near the patient's bed." (JTX 101 at 155161; Tr. 863:12-19 (Myrdal)). In contrast, the Vidal described the later-developed etoposide without *any* side effects specifically attributable to polysorbate 80. (Tr. 863:20-864:7 (Myrdal); JTX 101). It also reported milder overall side effects, with only rare hypersensitivity (2% of cases) even without special premedication. (*Id.*)

34. At trial, Mr. Fabre admitted that he relied on the Vidal for Sanofi's own swap from Cremophor to polysorbate. (Tr. 465:13-15 (Fabre)). That fact is further confirmed by Sanofi's internal memorandum from 1988 when they were first formulating docetaxel:

> Cremophor is accepted less and less often by clinicians and registration authorities alike. . . . This is why Sandoz, having developed the anti-neoplastic drug teniposide with Cremophor, then developed an analog product from it called etoposide in Tween [polysorbate 80]. (JTX 162, at 1).

35. Dr. Myrdal agreed with this assessment. The Sandoz experience reported in the Vidal, by itself, would make it obvious to choose polysorbate 80 instead of Cremophor: "It would tell me, if I looked at them side by side, I would choose polysorbate 80." (Tr. 864:20-25).

7. Dorr Alone Made Obvious The Swap To Polysorbate 80.

36. The Sandoz experience also led Professor Robert Dorr to publish the same swap in 1988 to formulate a poorly water soluble anti-cancer drug called acronycine. (JTX 215, Dorr).

37. Acronycine had been previously formulated with Emulphor (another name for Cremophor). (Tr. 854:19-855:9 (Myrdal)). But Professor Dorr concluded that "an Emulphor-based solution should be avoided" due to its potential for hypersensitivity reactions. (JTX 215, at 32; Tr. 855:19-856:1 (Myrdal)). He solved the problem by swapping surfactants based on Sandoz's clinical experience, noting that while Cremophor in teniposide had been associated with hypersensitivity, "clinical etoposide studies" with polysorbate 80 had "not produced excessive local venous toxicities nor general hypersensitivity reactions." (JTX 215, at 38; *accord* Tr. 859:23-860:10 (Myrdal)). Dorr alone makes the claimed formulation obvious: "Dr. Dorr is specifically telling me the best choice is polysorbate 80." (Tr. 860:11-18 (Myrdal)).

38. Dr. Park did not rebut, and actually ***agreed*** with Dr. Myrdal's reading of Dorr:

> Q. You understand that the Sandoz experience with those two drugs taught Professor Dorr to switch away from Cremophor towards polysorbate 80. Correct?

A. I think so, yes.

(Tr. 1501:14-17; Tr. 1506:19-1507:3 (Park) (same)).

8. O'Dwyer Alone Made Obvious The Swap To Polysorbate 80.

39. Another article that independently teaches the surfactant swap is the 1984 article by Dr. Peter O'Dwyer, who attributed Sandoz's reduction in hypersensitivity to its swap from Cremophor to polysorbate 80, noting that "one explanation" for the "greater frequency of allergic reactions" to teniposide compared to etoposide "may lie in the formulation of these agents" because they use different surfactants. (JTX 102, at 960). Dr. Myrdal explained that O'Dwyer alone makes the claimed swap obvious: O'Dwyer teaches that "the polysorbate 80 formulation is much safer" and "would be the better choice." (Tr. 860:22-862:3; 862:7-14 (Myrdal)).

B. Proposed Conclusions Of Law On Anticipation And Obviousness.

1. The Controlling Legal Standards For Anticipation And Obviousness.

40. Anticipation occurs where a single prior art reference discloses all of the elements of an asserted claim either expressly or inherently. 35 U.S.C. § 102; *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342 (Fed. Cir. 1999).

41. Obviousness occurs where a single prior art reference may not disclose all of the elements of an asserted claim, but the differences between the prior art and the claim would be obvious to a person of ordinary skill in the art.[2] 35 U.S.C. § 103; *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 427 (2007); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

42. The Supreme Court in *KSR* changed the legal landscape. Obviousness is now judged under "an expansive and flexible approach" driven by "common sense," and thus,

[2] The parties "generally agree" that a person of ordinary skill in the art could have a bachelor's or master's degree with several years of practical formulation experience, or a Ph.D. with fewer years of practical formulation experience. (Tr. 833:1-18 (Myrdal); 1437:10-15 (Park)).

patentability requires "more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 415-18. "[W]hen a patent claims … the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *Id*. at 416.

43. Though in this case the simple substitution of polysorbate 80 for Cremophor is the epitome of obviousness, at minimum this easily satisfies the Supreme Court's "obvious to try" standard: "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id* at 421; *see also In re Kubin*, 561 F.3d 1351, (Fed. Cir. 2009); *Bayer Schering AG v. Barr Labs., Inc*., 575 F.3d 1341, 1350 (Fed. Cir. 2009) (affirming obviousness where prior art "funneled" choices to only limited options).

44. While a patent is presumed valid and the challenger has the burden to rebut that presumption,[3] that burden "may be more easily carried" out using prior art references that were not before the Patent Office. *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp*., 225 F.3d 1349, 1356 (Fed. Cir. 2000). Here, almost *none* of the asserted prior art was before the Patent Office, including GV, Dorr, O'Dwyer, and Vidal.

2. The Alleged Core "Invention" Of Swapping Cremophor For Polysorbate Was Both Anticipated And Obvious.

45. All of the asserted claims are invalid based on the most fundamental principles of anticipation and obviousness. The core alleged "invention" here was nothing more than substituting one surfactant (Cremophor) for another (polysorbate 80). (Tr. 461:8-10 (Fabre); Tr. 636:23-637:5 (Kaler); JTX 3, '561 patent, 2:23-25).

[3] While Defendants understand the current case law to support a clear and convincing standard, the proper standard under the law for invalidity is a preponderance of the evidence which should be applied in this case, especially because prior art cited in litigation was never considered by the Patent Office. *See KSR*, 500 U.S. at 426. An application of the preponderance of the evidence standard is therefore requested.

46. GV blatantly anticipated the swap to polysorbate 80. (JTX 93, at 996). Before trial, Sanofi's *sole* argument was that GV disclosed an *in vitro* solution. During trial, Dr. Park ultimately agreed with Drs. Myrdal and Williams that GV was clearly not discussing an *in vitro* solution. (Tr. 842:7-24 (Myrdal); Tr. 1191:14-1192:5 (Williams); Tr. 1462:25-1463:3 (Park)).

47. Even if not anticipated, the claimed surfactant swap was exceedingly obvious. Under *KSR*, a patent is invalid as obvious when it claims nothing "more than the predictable use of prior art elements according *to their established functions.*" *KSR*, 550 U.S. at 417 (emphasis added). That is exactly what Sanofi is claiming here, as Dr. Kaler touted:

> Q. What's the magic or the gee whiz, as Mr. Hurst referred to, with respect to the '561 patent?
>
> A. It's the fact that you have polysorbate 80 molecules that carry docetaxel.
>
> Q. And keep it stable long enough to be perfused?
>
> A. That's what makes the invention of work. The presence of these micelles.

(Tr. 636:24-637:6 (Kaler)). He merely described how a surfactant works, which is, in fact, the long "established function" of polysorbate 80. (Tr. 1228:22-1229:1 (Williams); Tr. 852:2-18 (Myrdal)). Sanofi's other experts agreed. (Tr. 1516:14-16 (Park); Tr. 727:10-16 (Myerson)).

48. In addition to being polysorbate 80's established function, the prior art *expressly* and unanimously taught the swap from Cremophor to polysorbate 80 in multiple references, the GV, Vidal, Dorr, and O'Dwyer references discussed above.

49. Sanofi really had no response to any of this. In internal memoranda, Sanofi had already admitted that the prior art taught that "Cremophor is accepted less and less" and this is "why Sandoz…then developed an analog product" using polysorbate 80 instead. (JTX 162, at

1). And Dr. Park admitted that "the Sandoz experience" had "taught Professor Dorr to switch away from Cremophor towards polysorbate 80." (Tr. 1501:14-17 (Park)).

3. Sanofi Had No Legitimate Response To The Glaring Obviousness Of Swapping Cremophor For Polysorbate 80.

50. None of Sanofi's efforts to salvage its patents have any merit.

a. Pharmaceutical Formulators Do Not Ignore Formulations For Dissimilar Structures.

51. In an effort to avoid some of the art, such as Dorr and O'Dwyer, Sanofi argued that formulators only consider references about structurally related compounds. This ignores the prior art discussing docetaxel (GV and the '470 patent) and related taxanes (Tarr and the Miller '221 Patent). (*See generally* JTX 93, GV; JTX 9, '470 patent; JTX 16, Tarr; JTX 135, Miller).

52. It is also flatly untrue. As Dr. Myrdal explained, formulators routinely consider formulations for drugs "that are not related at all with respect to their chemical structure," because they "just need to look at the overall properties, how insoluble it really is." (Tr. 856:21-858:1 (Myrdal); *accord* Tr. 1204:21-1205:3 (Williams) (same)). This is confirmed by the references cited during this case. For instance, Professor Dorr followed Sandoz's etoposide work for acronycine, another insoluble anti-cancer drug, even though they are completely different structurally. (Tr. 856:21- 858:14 (Myrdal)). Another reference authored by Dr. Yalkowsky (the Tarr reference) likewise used the same formulation for three cancer drugs that were completely different structurally. (Tr. 1180:10-1182:5 (Williams)).

b. Nobody Thought Cremophor Was "Essential" To Docetaxel's Activity, and There Was No Teaching Away.

53. Sanofi next argued that formulators thought Cremophor was "essential" to the biologic activity of taxanes and, thus, swapping to polysorbate 80 would not have been obvious. (Tr. 1507:5-8 (Park)). The argument has no merit.

54. First, the Miller '221 patent directly refutes Sanofi's argument. That patent reports significant anti-cancer activity in live animals using a *Cremophor-free* formulation with polysorbate 80 for two *taxanes*: cephalomannine and taxol, proving that Cremophor is *not* essential . (JTX 135, Miller '221, at 7:1-15; Tr. 1168:19-1171:5 (Williams)).

55. Second, multiple prior art references taught formulating taxanes *without* Cremophor. This includes Miller (paclitaxel and cephalomannine) (JTX 135, at 7:1-15), Tarr (paclitaxel) (JTX 16, at 31), and GV (docetaxel) (JTX 93, at 996). Why would all of these prior art references teach using polysorbate 80 if the scientific community believed Cremophor was essential? Sanofi never offered an answer.

56. Third, Sanofi failed to offer a single prior art reference drawing *any* connection between Cremophor and a taxane's activity. Instead of relying on the prior art, Sanofi strangely relied on what was merely an obvious mistake by the authors of the 2001 van Zuylen reference – *published a full ten years after the critical date.* (PTX 209, at 125). True, the van Zuylen paper suggests that Cremophor could be important to the biological activity of paclitaxel (not docetaxel). (PTX 209, at 135). But in support, van Zuylen cited only the Rose paper from 1992, which is also not prior art, and which says the exact opposite of Sanofi's contention. (JTX 94, at 317; Tr. 866:15- 869:1 (Myrdal)). In plain English, Rose teaches that there is *no difference* in performance between polysorbate 80 and Cremophor: "taxol achieved similar maximum effects using either vehicle." (JTX 94, at 317).

57. The only article from before 1992 that Sanofi relied on was the Weiss paper, which also does not state Cremophor is essential to biological activity. Instead, it merely states that "[a]t present, there is no suitable substitute for Cremophor EL in taxol formulation." (JTX 145, at 1267). While true – the only available formulation of paclitaxel at the time did use

Cremophor EL – the statement says nothing at all about whether Cremophor itself is essential to paclitaxel's (much less docetaxel's) biological activity. (Tr. 219:1-8 (Burris); 996:11-21 (Calvert)). Moreover, Weiss is not a formulation paper, it does not mention polysorbate 80, and it fails to cite the Miller '221 patent.[4] (Tr. 217:17-23 (Burris); JTX 145, at 1263, 1268).

58. Sanofi also cited the Douros article (PTX 334, at 170) to attempt to undermine the Miller patent's crystal clear teaching that Cremophor is *not* essential and polysorbate 80 worked. Douros paclitaxel testing presumably formulated in Cremophor (the paper does not say), and reports results slightly higher than the data reported in Miller with polysorbate 80. (Tr. 1280:16-1285:1 (Williams)). From this, Sanofi argued that the references when put together taught away from using polysorbate 80.

59. This argument fails. The data from the two sets of experiments came from testing with different mice by different researchers at different times using different doses on different schedules. (Tr. 1511:13-1512:11 (Park); Tr. 1283:7-1285:1 (Williams)). Given all these differences – including a dosing difference of "almost ten times" – Dr. Williams explained, "it's not good science to directly compare the specific data" between Douros and Miller. (Tr. 1283:7-1284:19 (Williams)). Even Dr. Park "was not aware of any reference comparing these two tests in the way [he] compared them in court." (Tr. 1511:13-16 (Park)).

60. In the end, Sanofi relied mostly on the naked testimony of Dr. Burris, who said people "felt" Cremophor was essential to paclitaxel's biological activity. (Tr. 121:22-122:4 (Burris)). This testimony fails for three reasons. First, bare testimony about a recollection of what certain clinicians "felt" is not "prior art" under the Patent Act. Second, a medical doctor's view about what clinicians "felt" is doubly irrelevant because the person of ordinary skill in the

[4] Similarly, while Dr. Park testified that Cremophor's "inhibiting PGP" and "multidrug resistant" aspect made it essential, he agreed the prior art showed the same was true for polysorbate 80. (Tr. 1512:16-24, 1515:4-16 (Park)).

art is a formulator. Third, Dr. Burris was simply incorrect. As Defendants' expert Dr. Calvert explained, he "never heard a suggestion that it was for some reason essential to put Cremophor in." (Tr. 994:5-10 (Calvert)). And he was in a position to know because during the relevant time in the 1980s, while Dr. Burris was still in medical school, Dr. Calvert was *personally* working with the National Cancer Institute on Taxol clinical trials. (Tr. 993:3-10 (Calvert)).

c. Taxol Did Not Require Reformulation, Because Premedication Worked.

61. Sanofi also argued that using polysorbate could not have been obvious, because otherwise, formulators would have immediately swapped out Cremophor for polysorbate 80 when Taxol hypersensitivity reactions first surfaced in 1983.

62. That is not true. As the Kris publication explained, there were at least *three* alternative solutions to this problem: "pretreatment regimens, alternative schedules, or a reformulated preparation." (PTX 553, Kris, at 607). Clinicians tried premedication first, which immediately solved the problem by successfully managing hypersensitivity and that solution is still used today. (Tr. 215:2-20 (Burris); Tr. 1189:5-13 (Williams)).

63. In contrast to the easy solution of using premedication, reformulating paclitaxel would have set back work on an important cancer medicine for "several years." (Tr. 994:25-995:14 (Calvert)). Dr. Calvert – who, again, was actually involved in paclitaxel clinical trials at the time – explained that nobody "wanted to stop the momentum and back off in using this drug for the several years it would have taken to undertake a reformulation exercise." (*Id*.) Reformulation, after all, "would require that all of the preclinical and clinical testing would have to be done over again." (Tr. 1188:7-1189:4 (Williams)).

64. Any such reformulation effort also could have been a wasted effort. As Kris reported, nobody knew whether Cremophor (as opposed to paclitaxel itself) was causing the

hypersensitivity. (PTX 553, Kris, at 607). Accordingly, the fact that formulators in 1983 did not swap Cremophor for polysorbate 80 with the existing Taxol formulation says nothing about whether that swap was obvious when formulating a new drug in 1991.

d. Polysorbate 80 Was Known As Reasonably Safe, And Safer Than Cremophor.

65. Sanofi's final argument was that using polysorbate 80 was not obvious because skilled formulators thought polysorbate 80 would be unsafe in the levels used in the Taxotere product. That argument, too, fails for multiple reasons.

66. First, the asserted claims do not require any particular amount of polysorbate 80, much less the amount that Sanofi uses in Taxotere. Second, as Dr. Calvert explained, there was simply no "concern about the safety of polysorbate 80" in the prior art, which was a common ingredient in injectable products. (Tr. 995:15-996:4 (Calvert); Tr. 1369:6-1370:25 (Rodricks)). Even Sanofi's toxicologist admitted there was a "reasonable expectation" in 1991 that at least "some amount" would be safe. (Tr. 1371:13-17, 1373:1-6 (Rodricks)). Third, any doubt about using large amounts of polysorbate 80 (something the claims do not even require) is put to rest by the fact that "five times" *larger* amounts of Cremophor, a less safe surfactant, had been used with Taxol. (Tr. 862:7-14, 852:21-853:19, 924:4-21 (Myrdal)).

67. To nevertheless attempt to create safety issues where none existed, Dr. Rodricks implied that polysorbate 80 in E-Ferol may have caused deaths in infants who had "pre-existing respiratory distress." (Tr. 1330:21-1331:19; 1362:1-11 (Rodricks)). But he then freely admitted that "it was unclear how this happened, why it happened" and "it's still unclear what contributed to this." (Tr. 1331:10-19 (Rodricks)). The deaths easily could have resulted from "very high levels of Vitamin E itself" in E-Ferol, which Dr. Calvert explained can easily cause serious problems for "very sick, premature infants" (Tr. 999:25-1000-14 (Calvert)). Or the deaths could

have been the result of "contaminated polysorbate," something Dr. Rodricks admitted nobody could determine "one way or the other." (Tr. 1363:5-14 (Rodricks)). The E-Ferol incident thus raised no concerns about polysorbate 80's safety, particularly for adults.

C. Sanofi Made No Effort To Salvage Its Patents Based On The Various Extraneous Claim Limitations Beyond The Surfactant Swap.

68. In addition to the swap to polysorbate 80, some claims have other extraneous limitations. But Sanofi did not even try to salvage its patents based on those other limitations.

69. Dr. Williams went through the claims on an element-by-element, claim-by-claim basis. And for each and every claim, he found the claims to be independently anticipated and/or obvious over various prior art references and combinations. Sanofi never responded.

70. For example, claim 33 of the '512 patent requires a concentration limitation of docetaxel "from 10 to 200 mg/ml." Concentration levels are measured with a solubility study, which Drs. Myrdal and Williams explained is a "routine experiment" where formulators "put the drug in there, let it mix a while." (Tr. 888:16-819:10 (Myrdal); *accord* Tr. 1193:5-1194:14 (Williams)). Sanofi's own lab technician agreed that solubility testing is "basic," "like putting sugar into coffee." (Tr. 1301:9-14 (Rortais)). And Sanofi's own data showed that docetaxel inherently has a concentration in polysorbate within the claimed 10 to 200 mg/ml range. (Tr. 1194:17-1195:11 (Williams)). Sanofi never offered any contrary evidence.

71. In addition to being invalid over the prior art, claim 33's concentration range of up to "200 mg/ml" is invalid for lack of enablement. "[W]hen a range is claimed, there must be reasonable enablement of the scope of the range." *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). A claim is not enabled if the specification "expressly teaches against" what is required to make the invention work. *Id*. at 1244-45. Here, the '512 patent expressly "teaches against" using high levels of ethanol, such as the 50% in the prior art, which

is indisputably the only way of achieving the upper end of the clamed range of between "10 and 200 mg/ml." (JTX 1, '512 Patent, at 3:28-33; Tr. 892:7-24 (Myrdal)). Indeed, using "low ethanol content" is the "whole point of the ['512] patent." (Tr. 889:14-21 (Myrdal)).

72. As another example of an extraneous limitation, claim 7 of the '512 patent requires the formulation to be "essentially free or free of ethanol." For a stock solution, Sanofi admits that the element is disclosed in the '470 patent example, which used 5% ethanol. (Tr. 706:16-707:11 (Myerson)). The Tarr reference, too, disclosed stock solutions having from 0 to 30% ethanol, corresponding to perfusions with 0 to 1.2% ethanol. (JTX 16, Tarr, at 31; Tr. 1180:4-8 (Williams)). And under Sanofi's expansive construction of "essentially free" for a perfusion, that would cover perfusions made even from GV's 50% ethanol formulation, given enough dilution. (Tr. 1177:22-1178:13 (Williams)). Sanofi never denied these facts.

73. Because Sanofi never challenged Dr. Williams' opinions on all of these extraneous claim limitations, they should be deemed undisputed. *See Pfizer v. Apotex*, 480 F.3d 1348, 1360 (Fed. Cir. 2007 ("the patentee has the burden of going forward with rebuttal evidence"). Defendants have summarized the prior art evidence in the charts attached as Exhibits A through D (included within Defendants' 55-page limit).[5]

74. The one extraneous element that Sanofi attempted to address was the '561 patent limitation "without anaphylactic or alcohol intoxication manifestations." However, there is simply no possible claim construction that avoids the prior art while capturing Defendants' products. (*See infra* Section III.A.). Thus, the claims are either invalid or not infringed. "[T]hat

[5] If claim 5 of the '512 Patent is not invalid over the prior art, and if zero polysorbate is not "less than 35 ml/l" then claim 5 is not enabled. 35 U.S.C. § 112, ¶ 1. The '561 Patent does not disclose any lower limit or any basis to determine one. (JTX 3; Tr. 1162:6-1163:8 (Williams)). Additionally, if the claim is understood to have a non-zero lower limit, the claim is indefinite because such limit is not defined. 35 U.S.C. § 112, ¶ 2.

which would literally infringe if later in time anticipates if earlier." *Schering Corp. v. Geneva Pharms., Inc*., 339 F.3d 1373, 1379 (Fed.Cir.2003) (citations omitted).

75. Indeed, Sanofi's own witnesses admitted that the hypersensitivity statistics are about the same when comparing the prior art formulations (Taxol with Cremophor) to the claimed formulations (docetaxel with polysorbate 80) – less than 1% anaphylaxis and about 2% "severe hypersensitivity" for both products. (Tr. 1108:17-24, 1125:22-1126:21 (Childs); Tr. 1153:18-1154:5 (Williams); *accord* Tr. 1007:8-16, 1014:7-21 (Calvert); Tr. 220:1-17 (Burris)). And alcohol intoxication is similarly avoided in both formulations. (Tr. 231:22-232:12 (Burris)).

D. Instead Of Confronting The Evidence Based On The *Actual* Claims, Sanofi's Expert Added Limitations For "Safety, Efficacy, And Stability".

76. Sanofi never actually challenged Dr. Williams' invalidity opinions based on an element-by-element comparison. Instead, Sanofi asked Dr. Park for a sweeping conclusion about the validity of each claim, here for anticipation (and the same for obviousness):

> Q. Now that we have covered all the references cited by the defendants in their invalidity case, in your opinion, do any of these references anticipate the asserted claims of the '561 and the '512 patents?
>
> A. As we went through, none of the prior art anticipates the claims of the '512 or '561 patent. (Tr. 1489:21-1490:1 (Park)).

77. But Dr. Park based his entire opinion on an interpretation of the claims that defies their plain text and this Court's claim construction:

> Q. But for Claim 7 of the '512 patent, it claims a formulation, does it not?
>
> A. It's a composition.
>
> Q. Right. And did you consider safety and efficacy to be a requirement of the claims when you did your analysis of anticipation and obviousness?
>
> A. Right. Safety, efficacy, and stability.

> Q. If I asked you all five claims, you would give me the same answer, that when you evaluated anticipation and obviousness, you believed each claim required safety, efficacy, and stability. Correct?
>
> A. Correct. (Tr. 1491:25-1492:11 (Park)).

78. Dr. Park assumed the claims require "the maximum tolerated dose must be above the minimum effective dose." (Tr. 1491:5-9 (Park)). This might be an issue that the FDA addresses based on human clinical testing, but is not a claim term. (Tr. 927:19-928:1 (Myrdal)).

79. Dr. Park's analysis was tantamount to offering no rebuttal opinion at all. None of the claims mention anything about efficacy, stability, or safety (aside from avoiding alcohol and anaphylactic manifestations). Dr. Park added these noting that "we are talking about formulations that are *used* in human patients," but the asserted claims are compositions, and do not require any methods of *use*. (Tr. 1472:8-14 (Park)).

80. Except for one claim – claim 5 of the '561 patent – Sanofi did not and cannot argue the claims require safety, efficacy, and stability. For claim 5, it argued these limitations were *implicitly* included only because of the word "perfusion." (Tr. 1491:1-4 (Park)).

81. But as Dr. Myrdal explained, a "perfusion" is simply an injectable pharmaceutical solution, something that "goes out of the needle." (Tr. 929:9-16 (Myrdal); *accord* Tr. 1214:14-18 (Williams)). He also explained that the word "perfusion" applies to any such solution, *regardless* of whether it later turns out to be completely ineffective or toxic. (Tr. 929:9-21(Myrdal)). Dr. Calvert agreed, noting that this definition is consistent with the NCI definition of the synonym infusion ("a method of putting fluids including drugs into the bloodstream"). (Tr. 1031:24-1032:22 (Calvert); HTX 357, at 17 (NCI Glossary)).

82. Even Dr. Park agreed. The '470 patent used the term "perfusion" to describe a docetaxel formulation even before Sanofi "determined whether docetaxel would be safe and effective," yet Dr. Park agreed that "was a proper use of the word perfusion" (Tr. 1493:21-

1494:12 (Park)). Dr. Burris agreed too, admitting that it was proper to call Taxol a "perfusion" even though it has "caused death" and "sometimes . . . does not make a difference" in treating a patient's cancer. (Tr. 236:2-18 (Burris)).

83. In the end, Dr. Park's efforts to defend the validity of the patents by *adding* limitations is precluded not only by common sense, but also by the Federal Circuit's recent opinion in *Iovate Health Scis. v. Bio-Engineered Supplements & Nutrition, Inc.*, 2009 WL 3855928 (Fed. Cir. Nov. 19, 2009). There, like here, the patentee sought to read an "effectiveness requirement" into the claims. *Id*. at *4. The Court rejected that effort, noting that "[t]he claims also do not require any further measurement or determination of any result achieved by administering the claimed composition." *Id*. Of course, even if the claims had these limitations, the prior art would still invalidate them (including the GV reference that disclosed the claimed formulation, and substantial prior art with polysorbate 80 in clinical formulations).

E. Sanofi Failed To Establish *Any* Secondary Considerations, Which Cannot, In Any Event, Overcome Defendants' Compelling Evidence Of Obviousness

84. Sanofi's effort to overcome obviousness with secondary considerations failed. Especially in the wake of *KSR*, obviousness is found "even in the light of strong objective evidence tending to show non-obviousness." *Rothman v. Target Corp.*, 556 F.3d 1310, 1322 (Fed. Cir. 2009); *see also Leapfrog Enters. v. Fisher-Price*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Even before *KSR*, simple combinations like the one in this case define obviousness, despite substantial secondary considerations. *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483-84 (Fed. Cir. 1997) (combining known ingredients for known purposes).

1. Sanofi's Purported "Commercial Success" Is Unrelated To The Claimed Invention.

85. Commercial success is "only significant if there is a nexus between the claimed invention" and the secondary consideration at issue. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d

1299, 1311-1312 (Fed. Cir. 2006). Here, however, there is no nexus because Taxotere is not covered by the asserted claims. As Sanofi's own experts admitted: Taxotere has 12% ethanol so is not essentially free (Tr. 695:21-696:7 (Myerson)), it causes "Grade 4 allergic reactions, which would be anaphylaxis" (Tr. 208:16-21 (Burris)), and it includes water and citric acid, both of which affect stability for "consisting essentially of" claims (Tr. 593:2-10, 602:1-605:3 (Kaler)).

86. Moreover, "the asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art." *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). But Sanofi's own expert, Dr. Bokhart, admitted that he had "no independent opinion whether Taxotere would have been successful if the formulation used Cremophor instead of polysorbate 80." (Tr. 364:8-12 (Bokhart)). Nor could he, because there is no baseline comparator – that is, docetaxel formulated in Cremophor. (*Id.)* Plainly, the use of polysorbate 80 has *nothing* to with Taxotere's success, as Sanofi's director of marketing essentially admitted: "If you're asking specifically that I'm aware if anybody speaks about polysorbate 80, I've never seen that per se." (1083:23-1084:8 (Verini)). Instead, Dr. Bokhart acknowledged that docetaxel's "efficacy of curing cancer is the *primary driver* of Sanofi's sales of Taxotere." (Tr. 358:9-19, 367:6-16 (Bokhart); Tr. 1080:15-18 (Verini)).

2. No Evidence of Unexpected Benefits.

87. In addition to the lack of nexus explained above, Sanofi's purported unexpected benefits (such as potentially fewer drug-to-drug interactions) failed because it could not show they were *unexpected.* Under the law, the patent owner must first show "what properties were expected," and then show that the opposite occurred. *Pfizer v. Apotex*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). In *Pfizer*, for instance, the claimed unexpected benefits failed because "the record [was] devoid of *any* evidence of what the skilled artisan would have expected." *Id*.

88. That same is true here. Dr. Burris admitted for every purported "unexpected" property that "before polysorbate 80 was actually tested, there *wasn't any expectation* one way or the other about what would happen with it." (Tr. 201:9-203:8 (Burris)). He explained that each property "just had to be tested." (Tr. 201:3-203:8 (Burris)). Similarly, potential benefits such as alleged reduced neuropathy side effects, which Dr. Handy also addressed, suffer from the same problem because no evidence shows they were unexpected. (Tr. 1405:8-1407:4 (Handy)).

3. No Evidence of Long-Felt Need.

89. For "long-felt" need, Sanofi's only evidence was the hypersensitivity problems with Taxol, which Dr. Burris argued showed "they needed to find something other than Cremophor." (Tr. 127:17-128:155 (Burris)). That is false. Taxol's hypersensitivity reactions were fully managed by the use of premedication, which, of course, is a solution still in use even today in 2009. (Tr. 994:25-995:14 (Calvert); Tr. 1189:5-13 (Williams)).

4. No Evidence of Failure of Others.

90. Contrary to Sanofi's claim, there obviously was no evidence that anyone tried and failed to formulate docetaxel. The drug was patented, so only Sanofi itself had any incentive to formulate the drug. *See Sanofi-Synthelabo v. Apotex Inc.*, 488 F. Supp. 2d 317, 337 (S.D.N.Y. 2006) (discounting alleged failure of others where prior art compounds patented).

91. The *only* purported failure that Sanofi relied upon involved paclitaxel (not docetaxel) in the Tarr publication. But Tarr reported a success, not a failure. (JTX 16, Tarr, at 32; Tr. 1182:15-1183:9 (Williams)). Even Dr. Park acknowledged Tarr concluded that the "water-diluted mixture [like a perfusion] remains physically stable for at least three days and can also be infused intravenously at any desirable rate." (Tr. 1495:3-1496:4 (Park)). Though certain Tarr examples lasted only two hours, which may have been insufficient for paclitaxel (it

typically required at least 3 hours to administer), it was "sufficient" for the one-hour it took "to administer this drug [docetaxel] for a full dose to a patient." (Tr. 1183:15-1185:14 (Williams)).

5. No Evidence of Copying.

92. Sanofi's "copying" arguments were completely meritless because making generic versions of brand drugs "is what generic drug companies do" so the "copying argument is weak." *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, No. 2:05CV421, 2006 WL 2008962, at *45 (E.D. Va. July 17, 2006), *rev'd on other grounds* by 499 F.3d 1293 (Fed. Cir. 2007).

93. Moreover, neither Defendant "copied" Sanofi's product. They filed NDA B(2) applications, which are used where "there is something different about it relative to the ANDA product," such as a different formulation (Tr. 1054:14-1055:8 (Tao)). In fact, both Defendants offer substantially different products including, for instance, Hospira's one-vial system with two extra ingredients and Apotex's dissolution in only PEG 300, not mentioned in the patents.

III. The Asserted Claims Of The '561 Patent Are Invalid As Indefinite

94. All of the asserted claims of the '561 patent are invalid as indefinite, for two separate reasons. First, claims 2 and 10 purportedly are directed to a "composition," but they also improperly seem to include a method step ("is used to form"). Second, claims 2, 5, and 10 of the '561 patent are indefinite because they use a newly-coined but undefined term, "anaphylactic manifestations."

A. Proposed Findings Of Fact On Indefiniteness

1. The "Composition" Claims 2 And 10 Include A Method Step ("Is Used To Form")

95. Without rebuttal from Sanofi, Dr. Myrdal explained that claims 2 and 10 have no discernable scope to one of ordinary skilled in the art. The problem is that the claims are seemingly directed to a "composition," but then also seem to require a method step where that

"said composition is used to form an injectable solution." (Tr. 894:22-895:18 (Myrdal); JTX 3, '561 Patent, 3:40-60, 4:18-24). The question, then, is whether the claims cover a composition that must be actually used for the specified method. *Id.* Nothing in the patent and nothing in the prosecution history answers this question. (Tr. 894:1-4 (Myrdal)).

96. This raises an issue, for example, when the claimed "composition" as a stock solution "gets discarded because it expires" before being "used to form" an injectable solution. (Tr. 894:25-895:7 (Myrdal)). When asked whether any such discarded stock is covered, Dr. Myrdal concluded "I don't know if you have to do something with it or not." (Tr. 895:8-18 (Myrdal)). Sanofi offered no responsive testimony.

2. Sanofi's Coined Phrase "Anaphylactic Manifestations" In Claims 2, 5, And 10 Of The '561 Patent Has No Set Meaning.

97. The '561 patent coined the phrase avoiding "anaphylactic manifestations," which was included to attempt to distinguish the prior art. Sanofi's expert Dr. Handy confirmed that even though she had administered cancer drugs for over 30 years, she never heard the phrase "anaphylactic manifestations" outside the context of this patent litigation. (Tr. 1381:7-11; 1412:14-24, 1413:8-10 (Handy)).

98. Nothing in the patent defines the newly-coined term and, yet, its precise definition is critical. Sanofi relied on that term to attempt to distinguish the prior art. But there is no difference between the level of anaphylaxis or other severe hypersensitivity associated with Sanofi's Taxotere (polysorbate 80) and the prior art's Taxol (Cremophor). Both product labels have a prominent "black box" warning patients about "Severe hypersensitivity, including very rare fatal anaphylaxis" (JTX 70 (Taxotere) at 1) and "severe hypersensitivity reactions and …. fatal reactions." (JTX 64 (Taxol) at 1). Both labels require premedication, including dexamethasone steroid premedication, specifically to help manage anaphylaxis-type reactions.

(JTX 70 (Taxotere) at § 2.6; PTX 64 (Taxol) at "Dosage and Administration"). Finally, for both products there is less than 1% anaphylaxis and about 2% "severe hypersensitivity." (Tr. 1108:17-24, 1125:22-1126:21 (Childs); Tr. 1007:9-17, 1014:8-22 (Calvert)).

99. Given these realities, Sanofi did not propose any definition of "anaphylactic manifestations" that would distinguish between claimed docetaxel formulations (with polysorbate 80) and prior art paclitaxel formulations (with Cremophor). Nor could it.

100. First, a formulator does not understand what the term means except in the broadest sense of allergic reactions. (Tr. 893:16-22 (Myrdal); Tr. 635:7-16 (Kaler)). Second, even medical professionals disagree about "anaphylaxis" (much less the actual claim term "anaphylactic manifestations"). As Dr. Calvert explained, the symptoms for "anaphylaxis," Grade 4 hypersensitivity, "are the same as ones listed under Grade 3." (Tr. 1008:8-18 (Calvert)). The symptoms overlap. (Tr. 1096:11-20 (Childs)). There is only a subjective "difference in degree or a judgment call" and, in fact, "exactly the same treatment is given for Grade 3 or for Grade 4" reactions. (Tr. 1008:8-1009:13 (Calvert)). Some symptoms are even "subjective" depending upon "what the patient is experiencing." (Tr. 1413:23-1414:8 (Handy)). Third, Dr. Handy admitted that medical professionals did not really "get up to snuff on how to address anaphylaxis" until *after* Taxol was launched in 1992 – that is, *after* the patent applications in this case were filed and after Sanofi coined the term "anaphylactic manifestations." (Tr. 1418:2-1419:2 (Handy)). Even then, physicians did not agree on what qualifies as anaphylaxis, as evidenced by Dr. Burris resorting to his "I know it when I see it" approach (Tr. 114:5-6) and then disagreeing with Taxotere clinical investigators about whether patients with a particular set of symptoms actually experienced anaphylaxis. (Tr. 147:2-12 (Burris); Tr. 1012:3-14 (Calvert)).

101. Finally, the claim term is "anaphylactic *manifestations*," which focuses on *symptoms*, and it is undisputed that the "symptoms" of anaphylaxis and severe hypersensitivity are essentially the same. (Tr. 1014:24-1015:13 (Calvert); Tr. 1092:13-20 (Childs); Tr. 1413:11-22, 1415:17-1416:8 (Handy)). Moreover, the patent offers no guidance on what symptoms or "manifestations" are included under the claims, presenting a problem because, as Dr. Handy agreed, the "symptoms change throughout the literature." (Tr. 1413:18-22 (Handy)).

B. Proposed Conclusions Of Law On Indefiniteness

102. For indefiniteness, the "statutory requirement of particularity and distinctness in claims is met only when they clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1249 (Fed. Cir. 2008).

103. For the mixed composition/method elements of claims 2 and 10, the issue is controlled by the Federal Circuit's decision in *IPXL Holdings v. Amazon.com*, 430 F.3d 1377 (Fed. Cir. 2005). That case dealt with a similar issue about a claim having both a system and step where the "user uses" the system. *Id.* at 1384. The Federal Circuit invalidated the claim for reciting "both a system and the method for using that system." *Id*.

104. The *IPXL* reasoning applies here. As Dr. Myrdal explained, the mixed reference in claims 2 and 10 to a "composition" and the method step "whereby said composition is used to form" renders the claims indefinite. Just like the *IPXL* claimed "system" that a "users uses" was indefinite, so too is Sanofi's claimed "composition" that "is used to form."

105. The issue over "anaphylactic manifestations" is controlled by the Federal Circuit's decision in *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991), which held that "[w]hen the meaning of claims is in doubt, especially when, as is the case here, there is close prior art, they are properly declared invalid." *Id*. at 1218.

106. That is precisely the situation here because "there is close prior art" on the issue of "anaphylactic manifestations." Plainly, there is no meaningful definition of "anaphylactic manifestations" that threads the needle between two virtually indistinguishable products – the prior art Taxol (black box warning, premedication requirement, and less than 1% anaphylaxis) and the claimed Taxotere product (black box warning, a premedication requirement, and less than 1% anaphylaxis). Again, Sanofi failed to propose any construction to somehow thread this needle. To the contrary, *head-to-head* clinical trials comparing Taxol and Taxotere found no significant difference. (Tr. 1004:13-7, 1005:24-1006:6, 1014:8-22 (Calvert)).

IV. Claims 7 And 33 Of The '512 Patent Are Invalid For Double Patenting.

A. Proposed Findings Of Fact On Double Patenting

107. Claims 7 and 33 of the '512 Patent are invalid under the obviousness-type double pate*nting doctri*ne because these claims are not patentably distinct from claims 1, 11, and 44 of the earlier-issued '582 Patent. (Tr. 1164:12-1165:24 (Williams); ADX.1-30 – 1-32).

108. Neither the certified prosecution history of the '512 Patent nor publicly available information shows that a terminal disclaimer was recorded by the Patent Office.

B. Proposed Conclusions Of Law On Double Patenting

109. An obviousness-type double patenting analysis entails two steps. First, as a matter of law, a court compares the claim in the earlier and later patents. Second, the court reviews whether any differences are patentably distinct. A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting. *Eli Lilly & Co. v. Barr Labs*, 251 F.3d 951, 973 (Fed. Cir. 2001).

110. A terminal disclaimer can be filed in order to overcome a double-patenting problem. *Boehringer Ingelheim Int'l GmBH v. Barr Labs.*, 562 F. Supp. 2d 619, 630 (D. Del. 2008). A terminal disclaimer operates not only to "'tie the affected patents together' such that

they expire on the same date" but also ensure that they are "enforceable only during the time period in which they share the same owner." *Id*. But no such disclaimer was recorded here. Also, even if a terminal disclaimer were now recorded by the Patent Office, it should not allow Sanofi to overcome double-patenting because it was not cured at the time of trial. Equity weighs in favor of denying entry of any terminal disclaimer at this late date, after Defendants have expended substantial resources supporting this position through trial. *Id*. at 632 n.8.

V. The Asserted Patents Are Unenforceable Due To Inequitable Conduct.

A. Proposed Findings Of Fact On Inequitable Conduct

111. The '512 and '561 patents are unenforceable due to inequitable conduct and, in fact, the named inventor Mr. Fabre essentially admitted a violation of his duty of candor.

112. In September 1992, when applying for a patent in the United States, the applicants, including Mr. Fabre, signed a sworn declaration confirming that they had "a duty to disclose to the Office information they are aware of which is material." (JTX 4, at 12927). Mr. Fabre admitted at trial that he knew he had this duty of disclosure. (Tr. 474:22-475:10 (Fabre)).

113. Despite this, Mr. Fabre did not disclose what he admitted was his "main reference" for selecting polysorbate 80 to formulate docetaxel. (Tr. 477:10-478:5 (Fabre)). Specifically, when developing a docetaxel formulation, the Sanofi inventors recognized there was a problem with Cremophor because of its suspected hypersensitivity reactions, and Mr. Fabre was copied on a December 1988 memo with this understanding: "Cremophor is accepted less and less often by clinicians and registration authorities alike." (JTX 162, at 1).

114. Sanofi's inventors disclosed that known problem from the December 1988 memo to the Patent Office, citing Rowinsky for the hypersensitivity associated with Taxol: "anaphylactic manifestations are seen (see the publication by Rowinsky, page 1250, second column, last paragraph)." (JTX 3, '561 patent, at 1:60-64; Tr. 478:10-16 (Fabre)).

115. To solve this known problem, Sanofi copied the approach Sandoz had taken for its etoposide formulation – that is, swapping Cremophor for polysorbate 80. In the same paragraph of the same December 1988 internal memo, Sanofi memorialized that it was following Sandoz's approach: "This is why SANDOZ, having developed the antineoplastic drug TENIPOSIDE with CREMOPHOR, then developed an analogue product from it called ETOPOSIDE, in TWEEN [polysorbate 80]." (JTX 162, at 1).

116. Unlike the prior art relating to the ***problem***, however, nobody at Sanofi, including Fabre, told the Patent Office about their key prior art reference for the ***solution***. (Tr. 478:17-23 (Fabre)). There is no reference in the patent record to Sandoz's etoposide formulation, even though, just like the claimed formulation, it was for an insoluble cancer drug that used polysorbate 80 instead of Cremophor as the surfactant. (JTX 1, '512 patent; JTX 3, '561 patent; JTX 4, prosecution history; Tr. 463:17-24 (Fabre)). There is no dispute about the importance of Sandoz's prior art formulations. Mr. Fabre admitted it was one of the two main references for selecting polysorbate 80: "As I have already said, the main factors that shaped our thinking were the Sandoz experience and the taxol experience." (Tr. 477:10-478:5 (Fabre)).

117. There is no excuse for this failure. Fabre admitted that he learned about the Sandoz formulations simply by reading a standard reference book – the Vidal. (Tr. 465:13-467:18 (Fabre); D.I. 315, Appx. A (Uncontested Facts) at ¶156). Fabre "learned from [his] review of the prior art Sandoz compounds that you could substitute polysorbate 80 for Cremophor." (Tr. 467:19-22 (Fabre)). He also learned that etoposide formulated with polysorbate 80 "doesn't have any warnings," has "no reference to requiring strict medical supervision," and cites no "side effects that are specifically attributable to polysorbate 80." (Tr.

467:6-22). The Vidal is the same reference book Dr. Myrdal explained renders obvious, even by itself, the alleged core invention of swapping Cremophor for polysorbate 80. (Tr. 864:20-25).

118. In an effort to excuse concealing the Sandoz prior art, Mr. Fabre argued that his earlier reliance on "the Sandoz experience was invalidated by the tests that we carried out" later with "etoposide-type" formulations. (Tr. 475:16-23 (Fabre); JTX 60-T, at Appx. 12). For these experiments, Sanofi put docetaxel in the etoposide formulation and adjusted ingredient amounts – just the kind of "optimization" experiments both Dr. Myrdal and Dr. Williams described as routine. (926:4-16 (Myrdal); 1204:21-2105:21 (Williams)).

119. Sanofi's etoposide-type experiments cannot possibly excuse Mr. Fabre's concealment of the Sandoz prior art. First, Sanofi's etoposide experiments were internal *confidential* experiments, which hardly excuses the concealment of *published* prior art. For a patentability analysis, the disclosures in the published prior art are important, not private testing. What Fabre learned from the published Sandoz experience, but did not disclose to the PTO, is "that you could substitute polysorbate 80 for Cremophor." (Tr. 467:19-468:13 (Fabre)).

120. Second, Mr. Fabre's excuse rests on his claim that the "etoposide-type" perfusions were "failures" due to insufficient physical stability. (Tr. 446:4-12 (Fabre)). But the fact that perfusions could be made for ***any*** length of time still matches up with the claims. And even if the ***perfusions*** were considered a "failure," all but one of the claims (claim 5 of the '561 patent) cover either perfusions ***or stock solutions***, so should have been disclosed.

121. Third, Sanofi's "etoposide-type" formulations were actually successes, not failures. (Tr. 447:17-448:7 (Fabre)). During direct examination, Fabre mentioned only 14 of the 22 "etoposide-type" formulations they made. (Tr. 440:6-14, 443:5-24 (Fabre)). But ***13*** of those

were stable for a full hour (enough for the one-hour administration of docetaxel) and ***5*** were stable for at least four hours (matching Taxotere's label). (Tr. 447:22-448:7 (Fabre)).

122. Fourth, as it turned out, Sanofi had made another *eight* "etoposide-type" formulations that Fabre failed to mention on direct. (Tr. 440:6-14, 443:5-24 (Fabre)). These were even more stable, ranging from 5½ hours to 32 hours. (Tr. 450:10-17, 443:5-24 (Fabre)).

123. Mr. Fabre could not claim that these formulations were "failures." So, instead, he denied they were "etoposide-type formulations." (Tr. 445:13-446:6 (Fabre)), even though Sanofi's contemporaneous documents specifically called them "etoposide-type" formulations. (JTX 60-T, at Appxs. 7-9). Fabre acknowledged, for instance, that all eight formulations were included on memo pages where "the title is etoposide-side type formulation at the top." (Tr. 442:12-443:2, 491:15-17 (Fabre); JTX 60-T, Testing Report, at Appxs. 7-12). The materiality of these omissions and the unapologetic arguments at trial confirm deceptive intent.

124. Fabre's deceptive intent is further confirmed by a pattern of other misstatements and omissions. Sanofi falsely claimed in its patent specification – which Mr. Fabre admits he read and approved (Tr. 461:16-19 (Fabre)) – that "[i]n effect, when an injectable solution containing ethanol and a polysorbate 80 surfactant in place of Cremophor was used in the clinical situation [that is, the docetaxel formulation] it became apparent that the anaphylactic reactions were greatly reduced compared with the use of the same solution prepared with Cremophor." (JTX 3, '561 Patent at 2:25-30.)

125. At trial, Mr. Fabre admitted that the statement was false because a docetaxel solution in Cremophor had never been tested "in the clinical situation":

> Q. It says, in effect, when an injectable solution containing ethanol and a polysorbate 80 surfactant. Do you see that?
>
> A. Yes.
>
> Q. That's *docetaxel*; correct?

A. Yes.

***

Q. And *clinical situation* means in humans; right?

A. Yes.

Q. And the *same solution* is a reference back to the injectable solution on the first line; is that true?

A. Yes.

Q. But, in fact, you never tested a docetaxel solution prepared with Cremophor in humans; correct?

A. Yes. (Tr. 480:10-481:7 (Fabre)).

To this day, docetaxel has not been clinically tested in Cremophor. (Tr. 191:18-21 (Burris)).

126. Further confirming deceptive intent, Mr. Fabre also knew at the time he signed his patent declaration in September 1992 that anaphylactic manifestations ***were*** happening in clinical use with docetaxel formulated in polysorbate 80. (Tr. 483:2-484:17 (Fabre)). In fact, Mr. Fabre reviewed the March 1992 Investigator's Report only six months before signing his declaration (Tr. 482:2-24; 483:8-10 (Fabre) – a report that documents high levels (40% in one trial) of "anaphylactoid-type reactions" which is basically the same as the term in the patent, "anaphylactic manifestations." (*See* JTX 63 at 6.14; Tr. 483:2-484:14 (Fabre)). And yet, he claimed to the Patent Office that such reactions were "greatly reduced compared with the use of the same solution prepared with Cremophor." (JTX 3, '561 patent, at 2:25-30).

127. Finally, Mr. Fabre concealed the most damning art of all, GV, which specifically disclosed the claimed formulation. (JTX 93, at 996.) As project leader of Sanofi's Taxotere development, Mr. Fabre reviewed "the [GV] article with some care to make sure it was a proper article for the company to be publishing." (Tr. 469:11-20 (Fabre)).

128. As an attempt to justify concealing GV, Fabre claimed for the first time on *redirect* – when Sanofi knew there would be no further cross-examination – that he read *only* a March 1990 *draft* of the GV article that did not include the sentence disclosing the clinical

formulation. (Tr. 502:4-7; 503:6-503:15 (Fabre)). Between March 1990 and September 1992 (when he signed his patent declaration), Fabre claimed he *never* read a final draft of the March 1991 published GV article disclosing the clinical formulation. (Tr. 504:8-13 (Fabre)).

129. The notion that Mr. Fabre never read the final draft, even though he was personally responsible for approving what project details the company publicly disclosed, is simply not plausible. Indeed, the article was published in a highly prominent journal in March 1991, nineteen months before he signed his patent declaration, and reported to the world the clinical success of his polysorbate 80/ethanol formulation. (Tr. 471:11-24 (Fabre)).

130. In fact, while Mr. Fabre was *concealing* the GV reference from the Patent Office, he took steps in March 1992 to *disclose* the final version of GV (published a year earlier) to clinical investigators, since he was "unsatisfied" that the clinical brochure omitted the GV reference and thus "insisted" in a memo that it be cited. (Tr. 473:8-22; 478:24:479:3 (Fabre)).

131. Concealing such a highly material article from the Patent Office, while almost simultaneously taking steps to disclose it to clinical investigators, is inequitable conduct.

B. Proposed Conclusions Of Law On Inequitable Conduct

132. The asserted patents are unenforceable due to inequitable conduct. "[I]nequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *eSpeed, Inc. v. BrokerTec USA, L.L.C.*, 480 F.3d 1129, 1135 (Fed. Cir. 2007).

133. Materiality is judged under two complementary legal standards. First, information is material if it is not cumulative and it (a) establishes, by itself or in combination, a prima facie case of unpatentability; or (b) refutes or is inconsistent with a position the applicant takes in arguing for patentability. 37 C.F.R. § 1.56(b). Second, even if not within these categories, information is material if there is a substantial likelihood that a reasonable examiner

would have considered it important in deciding whether to allow a claim. *See Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1318 (Fed. Cir. 2006).

134. For intent, there "is no requirement that intent to deceive be proven by direct evidence; in fact, it is rarely proven by such evidence." *eSpeed*, 480 F.3d at 1138. Rather, "[t]he intent element of the offense is in the main proven by inferences drawn from facts, with the collection of inferences permitting a confident judgment that deceit has occurred." *McKesson Info Solutions, Inc. v. Bridge Med., Inc.*, 487 F.3d 897, 913 (Fed. Cir. 2007). For materially false statements, "[a]n inference of intent may arise where material false statements are proffered in a declaration or other sworn statement submitted to the PTO," such as the specification. *eSpeed*, 480 F.3d at 1138. For omissions, absent a credible explanation, "intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information." *Ferring B.C. v. Barr Labs*, 437 F.3d 1181, 1191 (Fed. Cir. 2006); *see also McKesson*, 487 F.3d at 915-16 (same); *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd*., 394 F.3d 1348, 1354 (Fed. Cir. 2005) (same).

135. This case involves textbook inequitable conduct. The asserted patents issued only after the inventors withheld critical prior art – the very Sandoz reference that gave them the idea to swap surfactants. They failed to tell the Patent Office that they copied the prior art for their idea to use polysorbate 80, instead claiming the idea as their own. The prior art is not cumulative of other disclosed art, which Sanofi distinguished on other grounds, as the Vidal taught using polysorbate 80 instead of Cremophor, and in commercially used products.

136. Mr. Fabre's deceptive intent is clear from the sheer materiality of the Sandoz prior art, including the Vidal. He admitted it was one of his two "main references," and was the very source for the idea to use polysorbate 80 instead of Cremophor. The Patent Office should have

been told about Sandoz's prior work so it could do its job, but it never had the chance. There simply is no justification for telling the Patent Office about the prior art disclosing the ***problem*** while concealing the prior art disclosing the ***solution***.

137. Sanofi's and Mr. Fabre's intent to deceive is further confirmed by the wide array of concealed information and misstatements, including the flatly false statement that Sanofi conducted clinical testing of docetaxel in Cremophor, the concealment of the GV reference which published the claimed formulation, and the concealment of clinical data contradicting the claim that clinical tests with polysorbate 80 "greatly reduced" anaphylactic manifestations.

138. This case thus falls squarely within a long line of Federal Circuit cases holding patents unenforceable in similar circumstances involving patterns of misconduct. *See, e.g., Nilssen v. Osram Sylvania, Inc.*, 504 F.3d 1223, 1235 (Fed. Cir. 2007) (even where applicant's failures not "per se unreasonable" "in isolation," patent unenforceable due to "repeated attempts to avoid playing fair and square with the patent system"); *Pharmacia Corp. v. Par Pharma., Inc.*, 417 F.3d 1369, 1373 (Fed. Cir. 2005) (finding inequitable conduct due to "highly material nature" of pattern of misconduct including the failure to submit key prior art). Both asserted patents, which are related, are unenforceable in view of this grave inequitable conduct.

VI. Defendants Do Not Infringe The Asserted Claims.

A. Proposed Findings Of Fact On Non-Infringement

1. Hospira's Product Is A Substantial Improvement.

139. The asserted patents discuss docetaxel formulations with only two inactive ingredients, ethanol and polysorbate 80. Hospira's Julie Liu tested a formulation with only those two ingredients, but it failed completely. In stability testing, the claimed formulation immediately began to destroy the docetaxel itself, showing "impurity of degradation products" of 0.9% even at the "initial time point." (JTX 36; Tr. 759:20-760:4 (Liu)). In accelerated stability

testing, the formulation tore apart docetaxel in four weeks, with a loss of 12.9% of the active at 40ºC and 33% at 50ºC. (JTX 108 at 5-6; Tr. 762:24-763:6, 766:15-767:12 (Liu)). Ms. Liu's "immediate reaction [was] this formulation is not going to be viable at all." (Tr. 760:2-15).

140. After extensive testing with multiple possible combinations, Ms. Liu settled on a formulation ("formulation 6") with two extra ingredients, citric acid and PEG 300. (Tr. 754:19-23, 755:18-756:13 (Liu); JTX 36 at 7). The result was a dramatic improvement in stability. In Ms. Liu's four-week stability studies, for instance, her new formulation experienced "almost no change, no degradation occurred." (Tr. 760:19-761:14; 762:24-763:6 (Liu); JTX 108 at 5-6).

141. Citric acid and PEG 300 enabled Ms. Liu to fix the many shortcomings of Sanofi's Taxotere. (Tr. 733:2-9, 787:4-6 (Liu)). First, Hospira's product is stable for *two years*, while Taxotere's "premix" is stable for only e*ight hours* before one has to "discard the solution." (Tr. 749:7-24 (Liu)). Second, Taxotere has to be sold as a "two vial product" instead of Hospira's convenient one vial. (Tr. 740:8-24 (Liu)). Third, Ms. Liu's formulation avoided the difficulty of mixing the two Taxotere vials together, which can produce either "lumps" of polysorbate 80 or "foaming," where "you're not going to end up with the exact amount of solution" necessary for accurate dosing. (Tr. 745:15-749:6 (Liu)).

142. Given the substantial improvements that Ms. Liu achieved, Hospira's extra ingredients are hardly "filler" as Sanofi claims. (Tr. 764:15-20 (Liu)). The Hospira product "is a single vial product, does not have the foaming problem, and it's stable for 24 months at room temperature." (Tr. 772:23-773:6 (Liu)). Hospira's formulation also uniquely allows multi-dose use, which "means that you can open the vial and use any required amount of the product, keep the remaining amount of product on the shelf, use it for next time." (Tr. 772:23-773:16 (Liu)).

143. The asserted '512 patent also requires a formulation that is "essentially free of ethanol." But just as Sanofi determined – given its own failed attempt to eliminate ethanol (Tr. 487:10-489:4 (Fabre)) – Ms. Liu determined that higher ethanol levels were necessary, and she used 23% ethanol. (Tr. 758:10-17, 774:12-775:9 (Liu)).

2. Apotex's NDA Product Is Two Vials on Which None of the Asserted Claims Read.

144. Apotex's NDA describes a docetaxel injection concentrate vial and a diluent vial. Sanofi does not allege that any asserted claim reads on either vial alone. (PTO Appx. B-1.) Rather, Sanofi alleges that the asserted claims read variously on (i) the intermediate dilution prepared from diluting the concentrate with the diluent—i.e., the premix—and (ii) a perfusion prepared from further diluting the premix with an I.V. bag of saline or glucose.

145. Apotex's injection concentrate is a concentrated solution. (Tr. at 719:21-22 ("Stock solution means it's a concentrated solution that will be diluted for further use."), 722:11-15 (Myerson)).

146. The premix made from Apotex's product is an intermediate dilution and it contains water, so it is not a concentrated solution. (Tr. 523:16-23 (Kaler) ("So in this '561 patent description of the stock solution, there's no water. Q. All right. A. So this is a stock solution.")). Because the premix made from Apotex's product is not a concentrated solution, it is not a "stock solution" under the Court's construction of that term.

3. Defendants' Products, Like Taxotere, Cannot Avoid Anaphylactic Manifestations.

147. The asserted claims of the '561 patent require formulations that avoid "anaphylactic manifestations." But unfortunately – like Taxotere – Defendants' products will cause severe hypersensitivity, including anaphylaxis (which Dr. Burris equated to "anaphylactic manifestations"). (Tr. 1031:8-13 (Calvert); Tr. 120:5-9, 207:10-209:17 (Burris)). Also like

Taxotere, Defendants' products will have a "black box" warning about these side effects, cautioning "severe hypersensitivity reactions characterized by generalized rash, erythema, hypertension and/or bronchospasm or, very rarely, fatal anaphylaxis in patients." (Tr. 176:8-17 (Burris); Tr. 986:4-987:3, 989:25-992:13, 1007:9-17 (Calvert); Tr. 1153:18-1154:5 (Williams)).

148. Although bizarre, Dr. Burris's proof that Defendants could ***avoid*** anaphylactic manifestations was "the part on Hospira's label that . . . says very rarely fatal anaphylaxis" occurs, which he concedes means that "sometimes, according to the label, Hospira's product will kill people." (Tr. 207:7-15 (Burris)). Sanofi admits that anaphylaxis (Dr. Burris' narrow view of "anaphylactic manifestations") ***will*** occur: "certainly less than two percent, probably less than one percent" of patients. (Tr. 179:15-180:1 (Burris); *accord* Tr. 1108:17-24 (Childs)).

149. In fact, Sanofi admits anaphylaxis will occur ***even with premedication*** (something mentioned nowhere in the '561 patent), and at least 0.6% of patients suffered from anaphylaxis viewed as a Grade 4 hypersensitivity reactions. (Tr. 208:16-210:22 (Burris); JTX 69, at 76). A "shock cart" must be on hand during Taxotere administration. (Tr. 984:10-985:2 (Calvert)).

150. For the reasons for premedication, Dr. Calvert explained that "steroids were first introduced during the Phase II trials in which I was participating, because of the accounts of hypersensitivity reactions." (Tr. 976:1-8 (Calvert); Tr. 1105:6-11 (Childs)). Sanofi's own testing summary confirms that "in an attempt to first decrease the incidence and severity of AHSR [hypersensitivity], various premedications were allowed." (JTX 69, at 22; Tr. 977:22-978:5 (Calvert)). The Taxotere product insert similarly reports that premedication is to address hypersensitivity reactions. (JTX 172, at 55; Tr. 982:9-983:8 (Calvert); Tr. 1100:14-16 (Childs)).

151. Contrary to Sanofi's assertion at trial, there is no question that Taxotere remains associated with anaphylaxis. In addition to the label itself, Sanofi's Dr. Handy relied upon her

"go to" reference, the Oncology Drug Nursing Handbook. (Tr. 1419:24-1420:4 (Handy)). On direct examination, Dr. Handy misleadingly referred to only part of the listing for Taxotere. (Tr. 1421:20-1422:7 (Handy)). On cross, however, she admitted that the rest of the same entry contained serious warnings about anaphylaxis, including "recall signs/symptoms of anaphylaxis and if these occur stop drug immediately and notify physician" and "teach patient the potential for hypersensitivity or anaphylactic reactions." (PTX 394, at 140; Tr. 1422:8-1423:21 (Handy)).

152. Symptoms associated with anaphylaxis include "bronchospasm, hypotension, abdominal cramping, and angioedema." (HTX 208, Craig Reference, at 286-87; Tr. 1018:4-1019:7 (Calvert)). The clinical data shows that these symptoms occur more frequently than anaphylaxis itself, in approximately 14% of Taxotere patients. (Tr. 1021:24-1022:13 (Calvert)).

B. Proposed Conclusions Of Law On Non-Infringement

153. Sanofi has the burden of proving that Defendants' B(2) products meet each and every limitation of any asserted claim. *Centricut LLC v. Esab Group*, 390 F.3d 1361, 1367 (Fed. Cir. 2004); *PSC Computer Prods., Inc. v. Foxconn Int'l*, 355 F.3d 1353, 1357 (Fed. Cir. 2004). Sanofi has not carried that burden.

1. Defendants Do Not Infringe Claim 7 Of The '512 Patent.

154. In construing claim 7 of the '512 Patent, the Court held that for a stock solution to be "essentially free" of ethanol, it can have "no more than 5% ethanol by volume." (JTX 179 at 2.) Hospira's stock solution has "23 percent ethanol," almost five times the allowed 5%. (Tr. 872:24-873:5 (Myrdal)); Tr. 696:8-21 (Myerson)). Assuming that Apotex's premix is a stock solution, as Sanofi contends, it also is not "essentially free or free of ethanol" because it has 6.3% ethanol. (ATX 552.0514; ATX 389.0006; Tr. 1145:7-13 (Williams); ADX.1-11.) Because both Defendants' accused stock solutions have "more than 5% ethanol by volume," neither meets the Court's construction of "essentially free" of ethanol. (JTX 179 at 2).

155. For a corresponding perfusion, the Court held that the claim requires "the same amount of ethanol as a stock solution with no more than 5% ethanol by volume." (*Id*.) Under a straightforward reading of this construction, neither Defendant infringes since the "amount" of ethanol in their perfusions is the "same amount" as their accused non-infringing stock solutions, because you do not "add or extract ethanol when you make a perfusion." (Tr. 874:23-25 (Myrdal); Tr. 697:24-698:7 (Myerson) (same)).

156. Hospira's stock solution has 23% ethanol and, therefore, the corresponding perfusion cannot possibly have the "same amount of ethanol as a stock solution with no more than 5% ethanol." (Tr. 873:13-874:16 (Myrdal)). Similarly, assuming that Apotex's premix is a stock solution as Sanofi contends, it has 6.3% ethanol, so a perfusion made from the premix also cannot possibly have "same amount of ethanol as a stock solution with no more than 5% ethanol." (ATX 552.0514; ATX 389.0006; Tr. 1145:7-13 (Williams); ADX.1-11).[6]

157. As Dr. Myrdal explained, this reading of the claims is fully consistent with the stated purpose of the ethanol-limitation, which is to avoid alcohol manifestations. (Tr. 888:16-889:21 (Myrdal); JTX 1, '512 patent, at 3:9-30). To define what qualifies as "too much" ethanol for this purpose, the '512 patent specifies a specific percentage of ethanol in the stock solution. (Tr. 885:12-887:4 (Myrdal); JTX 1, '512 patent, at 3:28-30). If it is too much in the stock solution, the "same amount" must be too much in the perfusion. (Tr. 875:1-876:24 (Myrdal)).

158. In contrast to this straightforward reading of the Court's claim construction, Dr. Myerson converted the Court's construction into an arbitrary cut-off of 1.85% ethanol for

[6] Claim 7 does not read on Apotex's injection concentrate because the injection concentrate does not contain polysorbate, a required limitation. (ATX 552.0412; ATX 552.0482; ATX 552.0514; Tr. 1141:3-1142:1 (Williams); ADX.1-9.) Claim 7 also does not read on a perfusion made from Apotex's NDA product where Apotex's docetaxel injection concentrate is the stock solution: ethanol is added to Apotex's injection concentrate to prepare the premix and, therefore, a perfusion prepared by a subsequent dilution of the premix does not contain the "same amount of ethanol" as Apotex's stock solution. (Tr. 1144:17-21, 1148:16-1149:5 (Williams); ADX.1-16.)

perfusions (even though the Court previously rejected Sanofi's proposed 2% construction). (D.I. 347 at n.3). In so doing, Dr. Myerson violated two fundamental rules of claim construction. First, he relied on the accused products to define "essentially free," even though it is black letter law that "a claim is construed in the light of the claim language…not in light of the accused device." *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1367 (Fed. Cir. 2008). Second, he relied on extrinsic sources for his flawed calculation. *Chamberlain Group, Inc. v. Lear Corp.*, 516 F.3d 1331, 1335 (Fed. Cir. 2008) (explaining that relying on extrinsic evidence is improper).

159. Specifically, to construe "essentially free" for perfusions, Dr. Myerson based his conversion calculation on "the docetaxel concentration" of an example in *the '470 patent*, which he admits is not even cited in the '512 patent. (Tr. 708:24-709:3, 714:25-715:18 (Myerson)). He then "took that stock concentration docetaxel and … divided by the perfusion concentration of docetaxel in … *Hospira's product*." (Tr. 709:11-18 (Myerson)). The same flawed analysis was done for Apotex's product as well. (Tr. 665:5-8, 673:15-674:20 (Myerson)). But, of course, Defendants' products are mentioned nowhere in the '512 patent. (Tr. 879:5-24 (Myrdal)). Similarly, Dr. Myerson applied a hypothetical dilution process, which accused Defendants of infringement by adding hypothetical dilutions that neither Defendant actually uses. (Tr. 1146:2-1148:2 (Williams); ADX.1-13; ADX.1-14).

160. The absurdity of Dr. Myerson's approach is highlighted by the fact that "essentially free" would change its meaning from lawsuit to lawsuit. (Tr. 880:12-881:2 (Myrdal)). "If the next defendant comes along" with "a different perfusion concentration," the meaning of "essentially free" would change to a ***different*** cut off. (Tr. 880:12-881:2 (Myrdal)). Similarly, if the '470 patent example happened to use 3 mg/ml of drug instead of 2 mg/ml, that too would change Dr. Myerson's view of "essentially free." (Tr. 712:15-713:4 (Myerson)).

161. To try to defend the indefensible, Dr. Myerson noted that under the Court's claim construction, one perfusion with a particular amount of ethanol might be "essentially free" while a different perfusion with the same amount of ethanol is not "essentially free." (Tr. 883:24-885:3 (Myrdal): Tr. 712:15-24 (Myerson)). That is true, depending on whether the corresponding stock solution is "essentially free." (Tr. 884:16-886:5 (Myrdal)). However anomalous that result, it is dictated by the fact that the '512 patent and claim construction define "essentially free" by the *percentage* of ethanol in the *stock solution*. (Tr. 886:21-887:4 (Myrdal)).

162. Defendants also do not infringe because claim 7 requires docetaxel "dissolved in polysorbate." In Apotex's docetaxel injection concentrate, docetaxel is fully dissolved in PEG 300. (ATX 552.412, 482, 514; Tr. 1151:6-7 (Williams); Tr. 719:9-12 (Myerson)). When the diluent is added to Apotex's docetaxel injection concentrate to make the premix, docetaxel remains dissolved in PEG 300, not polysorbate. (Tr. 1150:6-15, 1151:8-11 (Williams)). When the premix made from Apotex's product is diluted to make a perfusion, docetaxel remains dissolved in PEG 300, not polysorbate. (Tr. 1151:12-1152:12 (Williams)). The role of polysorbate in a perfusion is to form micelles that encapsulate docetaxel. (Tr. 1151:14-17 (Williams); Tr. 529:20-530:2 (Kaler); PDX 4-12). Thus, the docetaxel is not "dissolved" in polysorbate 80. Sanofi never proved otherwise, for either Apotex's or Hospira's formulations.

2. Defendants Do Not Infringe Claim 33 Of The '512 Patent.

163. Claim 33 of the '512 Patent requires a "stock solution" comprising docetaxel "dissolved in polysorbate." (See JTX 1; Tr. 676:6-10 (Myerson); ADX.1-19.) Claim 33 does not read on Apotex's premix, accused of infringing, because it is the result of a dilution with water (PTO Appx. A ¶ 60.) Thus, it is not a concentrated solution and not a "stock solution" under the Court's construction. Furthermore, claim 33 does not read on the premix made from Apotex's product because docetaxel is already dissolved in PEG 300 in Apotex's injection

concentrate in the first instance and is not later "dissolved in polysorbate" in the premix made from Apotex's product. (Tr. 1152:13-24, 1151:21-1152:3 (Williams)). Sanofi never proved that either Apotex's or Hospira's formulations are "dissolved" in polysorbate.

3. Defendants Do Not Infringe Claims 2, 5 Or 10 Of The '561 Patent.

164. Defendants do not infringe claims 2, 5, and 10 of the '561 patent. All of these claims require a formulation where there is "a reasonable expectation of being administered without causing anaphylactic manifestations." (JTX 3, '561 Patent, claims; D.I. 347 at B.5).

165. As Dr. Calvert explained, to the extent it has a discernable meaning at all, the term "anaphylactic manifestations" is broader than anaphylaxis itself, because it extends to the "multiple symptoms of anaphylaxis." (Tr. 1015:5-13 (Calvert)). Based on clinical data, that results in 14% of all patients suffering from some form of anaphylactic manifestations. (Tr. 1021:24-1022:13 (Calvert)). Thus, there is no reasonable expectation of avoiding them, and Defendants do not infringe claims 2, 5, and 10.

166. According to Dr. Burris, "anaphylactic manifestations" is really only limited to "anaphylaxis" itself, meaning symptoms associated with anaphylaxis do *not* qualify unless a physician subjectively concludes there is anaphylaxis. (Tr. 120:5-9 (Burris)). Even under that restrictive view, however, Defendants products will still cause anaphylaxis in at least 0.6% of patients, even with premedication. (Tr. 208:22-209:6, 210:20-22 (Burris); *accord* Tr. 1108:17-24 (Childs)). That "works out to about 1 in 170 patients." (Tr. 983:16-22 (Calvert)). Given the tens of thousands of Taxotere patients, there is certainty that Defendants' products *will* cause severe hypersensitivity, specifically including anaphylaxis, which explains the need for warnings and emergency equipment on hand. (Tr. 983:23-984:9, 990:15-22 (Calvert)). Thus, Defendants

do not infringe because there is no "reasonable expectation" of avoiding anaphylactic manifestations.[7] (Tr. 990:9-14 (Calvert); Tr. 1152:25-1153:15 (Williams)).

4. Defendants Do Not Infringe Claims 2 Or 10 Of The '561 Patent.

167. Claims 2 and 10 require formulations that "consist essentially of" polysorbate 80 and ethanol. Apotex adds PEG 300. Hospira adds both PEG 300 and citric acid. Under the law and the Court's claim construction, adding ingredients that "materially affect the basic and novel properties of the invention" avoids infringement. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1239 (Fed. Cir. 2003); (D.I. 347, at 3.)

168. There are three types of basic and novel properties of the claimed formulation: (1) a two-solvent system, (2) decreased ethanol without adding other ingredients, and (3) physical *and* chemical stability for *both* the stock solution *and* the perfusion. (Tr. 1155:15-1157:1, 1157:25-1158:4, 1158:18-1159:5 (Williams); Tr. 526:10-20; PDX 4-10 (Kaler)).

169. Regarding the first basic and novel property, neither Defendant uses a two-solvent system. They use three-solvent systems, which, by itself, avoids infringement. Sanofi specifically distinguished claims 2 and 10 on the basis that the claims "as written, 'consists essentially of' a two-solvent system," whereas the Tarr prior art used "a three-solvent system." (JTX 59 at 3-4; Tr. 1163:9-25 (Williams)). During patent prosecution, Sanofi claimed there was no evidence the Tarr formulation "would work" without its third solvent (pluronic L64), which made up "over half of its solvent base." (Tr. 586:2-21, 585:7-12 (Kaler); JTX 59, at 4-5.)

170. That is exactly the situation here. Both Defendants include PEG 300, admittedly a solvent, and used for over "half of its solvent base." (Tr. 576:21-23, 577:4-8 (Kaler); Tr. 1143:4-25; 1158:2-4; 1160:19-24 (Williams); ADX.1-24). There is no evidence either product "would work" without "over half of its solvent base." (Tr. 585:13-17 (Kaler)).

[7] For the same reasons, the asserted claims are not enabled, since the claimed side effects are not avoided.

171. Regarding the second basic and novel property, and providing another basis for non-infringement, Defendants' use of PEG 300 instead of ethanol reduces the amount of ethanol needed. (Tr.1156:24-1157:24 (Williams)). It is not disputed that PEG 300 has a different carrying capacity than other solvents, including ethanol and other alternatives such as the water that is used in Taxotere's premix. (Tr. 593:3-10 (Kaler)). Thus, adding PEG 300 affects the physical stability of the resulting formulation. (*Id*.) Similarly, as shown above, Sanofi did not prove that docetaxel is "dissolved in a mixture of ethanol and polysorbate" as required by claims 2 and 10. In fact, Apotex showed the docetaxel in its injection concentrate is dissolved in PEG 300, not polysorbate. (Tr. 1160:25-1161:5 (Williams)). Still, however, Defendants' formulations are not essentially free of ethanol, with Apotex having over 6% and Hospira 23%.

172. Regarding the third basic and novel property, and providing yet another basis for non-infringement, both Defendants add extra ingredients that affect physical and chemical stability. Both Defendants add PEG 300 and Hospira additionally adds citric acid. Sanofi effectively admitted that PEG 300 and citric acid make a material difference. Mr. Fabre admitted that "PEG in a formulation makes it different from [my] claimed invention." (Tr. 450:20-22 (Fabre)). As to the citric acid, Sanofi initially did not use citric acid, but later added it to create a "more ***physically and chemically*** stable formulation of docetaxel." (JTX 345, at S-19) (emphasis added). Sanofi even commissioned a specially-prepared grade of polysorbate 80 that added citric acid "made only for Sanofi-Aventis." (Tr. 121:24-1292:15; 1294:6-16 (Acott)). Similarly, Ms. Liu's experiments proved that a formulation *without* both these additional ingredients was a complete failure. (902:2-903:19 (Myrdal)).

173. To attempt to avoid the overwhelming evidence of non-infringement, Sanofi's expert Dr. Kaler opined that the *only* basic and novel property of the claimed formulation was

the "physical stability" (not the chemical stability) of the perfusion (not the stock solution). (Tr. 562:12-563:2 (Kaler)). Dr. Kaler admitted that Defendants' do not infringe if the Court rejects this restrictive view: "If somehow that were true, I think you're right." (Tr. 563:24-564:2 (Kaler)). This effort fails to establish infringement for multiple reasons.

174. First, Dr. Kaler illogically failed to identify *any* basic and novel properties for stock solutions, even though he says claim 2 is limited to stock solutions. (Tr. 558:24-559:7 (Kaler)). This makes no sense. The patent is plainly directed to *both* stock solutions *and* perfusions, so the basic and novel properties apply to *both*. (Tr. 899:4-25 (Myrdal)).

175. Second, contrary to Dr. Kaler's testimony, the '561 patent expressly confirms the importance of chemical stability, referring to a formulation "which is stable from both a physical standpoint and a chemical standpoint." (JTX 1, '561 Patent, a1:50-51.) It also specifically discussed in "Examples According To The Invention" the "physico-chemical stability of this [stock] solution is satisfactory." (*Id*, at col. 2, ll. 61-62; *accord* Tr. 899:4-900:8 (Myrdal)). In fact, during claim construction briefing, Sanofi stated that "the claimed formulations allow for a more physically ***and chemically*** stable perfusion." (D.I. 45, Sanofi's Claim Constr. Br., at 14.)

176. Third, as much as he tried to limit the basic and novel properties only to physical stability, Dr. Kaler stated that the claimed invention requires at least "adequate chemical stability." (Tr. 553:11-16 (Kaler)). And yet, Dr. Kaler acknowledged that Ms. Liu's data proved that PEG 300 and citric acid" "play an important role in improving the chemical stability." (Tr. 561:17-20 (Kaler); *accord* Tr. 770:4-19, 771:4-7 (Liu)).

177. Finally, even if the Court *were* to limit the claims as Dr. Kaler proposed, Sanofi's infringement case *still* fails. According to Dr. Kaler, the claims require a perfusion to be "physically stable for up to eight hours." (Tr. 527:10-13, 598:10-17, 599:17-19, 624:19-24

(Kaler)). Yet he did not know how long a perfusion made from either Defendants' product actually lasts, and never did any tests to find out. (Tr. 599:18-25, 611:18-23, 623:11-16 (Kaler)). In fact, in the only testing under "real-life conditions," Hospira's perfusion lasted six hours, but no longer. (JTX 47, at 10; Tr. 781:2-7, 786:3-9, 821:1-11 (Liu)).

178. Moreover, adding PEG 300 *does* increase the physical stability of the perfusion made from Hospira's product by about 33%. Sanofi never conducted any testing on the issue. (Tr. 560:15-23, 611:9-23 (Kaler)). Only Ms. Liu did so, and her testing showed that PEG 300 increased stability from about 4 ½ hours to "up to 6 hours." (JTX 47 at 10; Tr. 786:3-9. (Liu)).

5. Sanofi Failed to Prove Indirect Infringement.

179. For Hospira's perfusion, and for Apotex's NDA product, Sanofi alleges only indirect infringement. This requires proof of additional elements, such as intent to induce infringement (not just the infringing acts). At trial, an Apotex representative explained that Apotex will sell its NDA product to wholesalers and distributors, not to medical professionals, and that Apotex does not detail or instruct medical professionals on how to use the NDA product. (Tr. 1067:6-1069:2 (Tao)). Sanofi's only evidence of a specific intent to induce infringement is Defendants' proposed label. However, as a matter a law, a label alone is not enough to show specific intent in a Hatch-Waxman case like this one. *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1304 (Fed. Cir. 2006); *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003). Indeed, Defendants' label and prescribing information have yet to be approved by the FDA and are subject to change. (Tr. 1066:14-1067:2 (Tao)). And both Defendants designed-around the asserted claims, showing their intent *not* to infringe. Further, as to contributory infringement, Sanofi failed to prove that either NDA product was made knowing the same to be especially made or adapted to infringe. *Aro Mfg. Co., Inc. v. Convertible Top Co.*, 377 U.S. 476 (1964).

VII. Conclusion

180. The asserted claims are all invalid, unenforceable, and not infringed.

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Exhibit A: Claim 7 of '512 Patent

Claim 7	Obvious in view of GV and '470 Patent	Obvious in view of Tarr	Obvious in view of '470 Patent and Surfactant Swap Art
"A composition comprising [docetaxel],…"	**Not disputed in GV:** (JTX 93; GV at p. 996.)	Tarr used Taxol: (JTX 16; Tarr at p. 31.) Obvious to switch to docetaxel: Switching from Taxol to docetaxel "the simplest exercise, particularly between two taxanes, I think this is an incredibly obvious thing for a formulator to do." (Tr. 1182:11-14 (Williams)). "[T]he docetaxel to Taxol switch . . . very, very obvious." (Tr. 1186:22-24 (Williams)).	**Not disputed in 470:** (JTX 09; '470 Patent at col. 9, ll. 17-21.)
"said composition being dissolved in [polysorbate],…"	**Not disputed in GV:** (JTX 93; GV at p. 996.)	**Not disputed:** (JTX 16; Tarr at p. 31.)	'470 Patent used Cremophor (Emulphor): (JTX 09; '470 Patent at col. 10, ll. 5-7.) Swap art taught use of polysorbate 80 instead of Cremophor: Handbook of Pharmaceutical Excipients, Dorr, O'Dwyer, and Vidal. "[I]t was routine at that time to swap basically the two choices for surfactant at the time, which were Cremophor or polysorbate, one for the other." (Tr. 1187:11-19 (Williams)). "[I]t would have been an obvious thing to do based on what was available to me, especially considering the fact that docetaxel in particular was presented with an Emulphor-ethanol system, a surfactant/ethanol system, and a polysorbate 80/ethanol system also." (Tr. 870:15-19 (Myrdal)).
"said composition being essentially free or free of ethanol."	GV is Essentially Free if Dr. Myerson's dilution approach is accepted: "I think you need something like a 25, 27-fold dilution to get this magic number of 1.85%" which is not "an unusual dilution." (Tr. 1178:5-13 (Williams)). **Or obvious with '470, where it is not disputed:** (JTX 09; '470 Patent at col. 10, ll.7-8.) "Of course, it's a stock solution essentially free of ethanol" (Tr. 707:10-11 (Myerson)).	**Not disputed:** (JTX 16; Tarr at p. 31.)	**Not disputed:** (JTX 09; '470 Patent at col. 10, ll.7-8.) "Of course, it's a stock solution essentially free of ethanol" (Tr. 707:10-11 (Myerson)).

Exhibit B: Claim 33 of '512 Patent

Claim 33	Anticipated by GV	Obvious in view of GV and '470 Patent	Obvious in view of '470 Patent and Surfactant Swap Art
"A stock solution comprising [docetaxel],…"	**Not disputed:** (JTX 93; GV at p. 996.) "Since there is no water, the only thing it can be is a stock solution." (Tr. 1190:7-13 (Williams)).	**Not disputed in GV:** (JTX 93; GV at p. 996 and JTX 09; '470 Patent at col. 10, ll. 5-7.)	**Not disputed:** (JTX 09; '470 Patent at col. 10, ll. 5-7.)
"said compound being dissolved in [polysorbate],…"	**Not disputed:** (JTX 93; GV at p. 996.)	**Not disputed in GV:** (JTX 93; GV at p. 996.)	'470 Patent used Cremophor (Emulphor): (JTX 09; '470 Patent at col. 10, ll. 5-7.) Swap art taught use of polysorbate 80 instead of Cremophor: Handbook of Pharmaceutical Excipients, Dorr, O'Dwyer, and Vidal "[I]t was routine at that time to swap basically the two choices for surfactant at the time, which were Cremophor or polysorbate, one for the other." (Tr. 1187:11-19 (Williams)). "[I]t would have been an obvious thing to do based on what was available to me, especially considering the fact that docetaxel in particular was presented with an Emulphor-ethanol system, a surfactant/ethanol system, and a polysorbate 80/ethanol system also." (Tr. 870:15-19 (Myrdal)).
"wherein said stock solution contains from 10 to 200 mg/ml of [docetaxel]."	Greater than 10 mg/ml is an inherent property of the GV formulation: "It's not expressly disclosed, but it's an inherent solubility property of docetaxel, that you could easily get into that concentration range doing the most routine experiment the formulators would do." (Tr. 1193:14-17 (Williams)). (JTX 320; Sanofi Formulation 2 Development Report at p. 3.) "[S]olubility in dehydrated alcohol, which is ethanol, is 160 milligrams per ml. And in polysorbate 80, it's a hundred milligrams per ml. So the combination of the two, a person of ordinary skill would expect that the solubility in the one to one would be at least above 100." (Tr. 1195:1-9 (Williams)).	'470 Patent showed 20 mg/ml of docetaxel with Cremophor: (JTX 09; '470 Patent at col. 10, ll. 5-7.) "So the composition example, as shown here, starts out with the docetaxel dissolved in the Cremophor ethanol stock solution, one to one, at 20 milligrams per millimeter. So there, you're above ten in that system." (Tr. 1196:23-1197:1 (Williams)). "[B]oth Emulphor, which is Cremophor, and polysorbate, are both non-ionic surfactants ... And the solubility, if you switched the Cremophor from polysorbate, would not dramatically change." (Tr. 1197:13-18 (Williams)).	'470 Patent showed 20 mg/ml of docetaxel: (JTX 09; '470 Patent at col. 10, ll. 5-7.) "So the composition example, as shown here, starts out with the docetaxel dissolved in the Cremophor ethanol stock solution, one to one, at 20 milligrams per millimeter. So there, you're above ten in that system." (Tr. 1196:23-1197:1 (Williams)). "[B]oth Emulphor, which is Cremophor, and polysorbate, are both non-ionic surfactants ... And the solubility, if you switched the Cremophor from polysorbate, would not dramatically change." (Tr. 1197:13-18 (Williams)).

Exhibit C: Claims 2 and 10 of '561 Patent

Claims 2 and 10	Anticipated by GV	Obvious in view of '470 Patent and Surfactant Swap Art	Obvious in view of Etoposide (Kaler's View)
"A composition consisting essentially of [docetaxel],…"	**Not disputed:** (JTX 93; GV at p. 996.)	**Not disputed in '470:** (JTX 09; '470 Patent at col. 10, ll. 5-7.)	Obvious to use etoposide formulation with a poorly water soluble drug like docetaxel: "We just need to look at the overall properties… These are both poorly soluble compounds…So any approach we can use with one [drug] we will use for another." (Tr. 857:22-858:1 (Myrdal)).
"dissolved in a mixture of ethanol and a polysorbate…"	**Not disputed:** (JTX 93; GV at p. 996.)	'470 Patent used Cremophor (Emulphor): (JTX 09; '470 Patent at col. 10, ll. 5-7.) Swap art taught use of polysorbate 80 instead of Cremophor: Handbook of Pharmaceutical Excipients, Dorr, O'Dwyer, and Vidal "[I]t was routine at that time to swap basically the two choices for surfactant at the time, which were Cremophor or polysorbate, one for the other." (Tr. 1187:11-19 (Williams)).	Etoposide formulation used ethanol and polysorbate 80: (JTX0215; Dorr at p. 33.) If Dr. Kaler's view is accepted, PEG 300 and citric acid do not affect the basic and novel properties: "These additives [PEG 300 and citric acid] do not affect the size of the docetaxel -- of the polysorbate 80 micelle which is carrying the docetaxel….if these additives change the micelle size, I would imagine that they could have some effect on physical stability. They don't." (Tr. 539:9-16 (Kaler)). **Not disputed:** Benzyl alcohol does not affect properties (Tr. 591:4-16 (Kaler)).
"whereby said composition is used to form an injectable solution which contains up to about 1 mg/ml of [docetaxel],…"	GV's stock solutions can be made into perfusions: "The only thing it can be used for or useful for would be to form a perfusion in an aqueous solution." (Tr. 1200:3-7 (Williams)). Less than 1 mg/ml was already in the prior art: "[Rowinsky] states that it is necessary to limit the concentration of active principle in the perfusion solution to concentrations of approximately 0.03 to 0.6 mg/ml." (JTX 03; '561 Patent col. 1, ll. 46-55; *accord* Tr. 1201:3-18 (Williams)).	'470 Patent discloses diluting its docetaxel stock solutions to form perfusions: (JTX 09; '470 Patent at col. 10, ll. 9-11.) "[T]his composition, which is that two mg per ml composition, may be administered by introduction into an intravenous perfusion… So just dilution by a factor of two brings you from two mgs per ml to one mg per ml." (Tr. 1202:21-1203:13 (Williams)).	Dorr discloses that the etoposide stock solutions were diluted to form perfusions at 1mg/ml: (JTX0215; Dorr at p. 34.) Less than 1 mg/ml was already in the prior art: "[Rowinsky] states that it is necessary to limit the concentration of active principle in the perfusion solution to concentrations of approximately 0.03 to 0.6 mg/ml." (JTX 03; '561 Patent col. 1, ll. 46-55; *accord* Tr. 1201:3-18 (Williams)).
"said injectable solution being capable of being injected without anaphylactic or alcohol intoxication manifestations being associated therewith."	GV formulation had reasonable expectation of avoiding: If term is definite and rare manifestations are acceptable (as Sanofi argues for infringement), then a reasonable expectation was in the swap out prior art references just by using polysorbate 80, and all the more so with premedication. (Tr. 1108:17-24, 1125:22-1126:21 (Childs); Tr. 1007:9-17, 1014:8-22 (Calvert)). Same for alcohol intoxication. ((Tr. 231:22-232:12 (Burris); Tr. 1028:21-23 (Calvert)).	'470 formulation had reasonable expectation of avoiding:. If term is definite and rare manifestations are acceptable (as Sanofi argues for infringement), then a reasonable expectation was in the swap out prior art references by using polysorbate 80, and all the more so with premedication. (Tr. 1108:17-24, 1125:22-1126:21 (Childs); Tr. 1007:9-17, 1014:8-22 (Calvert)). Same for alcohol intoxication. (Tr. 231:22-232:12 (Burris); Tr. 1028:21-23 (Calvert)).	Etoposide formulation had reasonable expectation of avoiding: If term is definite and rare manifestations are acceptable (as Sanofi argues for infringement), then a reasonable expectation was in the swap out prior art references just by using polysorbate 80, and all the more so with premedication. (Tr. 1108:17-24, 1125:22-1126:21 (Childs); Tr. 1007:9-17, 1014:8-22 (Calvert)). Same for alcohol intoxication. ((Tr. 231:22-232:12 (Burris); Tr. 1028:21-23 (Calvert)).

Exhibit D: Claim 5 of '561 Patent

Claim 5	Anticipated by '470 Patent	Anticipated by Tarr	Anticipated by Rowinsky	Obvious in View of GV
"A perfusion,…"	**Not disputed:** (JTX 9, '470 patent at 10:9-11; *accord* Tr. 1493:24-1494:1 (Park)).	Tarr discloses a perfusion of paclitaxel: (JTX 16; Tarr at p. 31; *accord* Tr. 1214:10-13 (Williams)).	**Not disputed:** (JTX 15; Rowinsky at p. 1251.)	GV's stock solutions can only be made into perfusions: "The only thing it can be used for or useful for would be to form a perfusion in an aqueous solution." (Tr. 1200:3-7 (Williams)).
"which contains approximately 1 mg/ml or less of [paclitaxel or docetaxel],…"	'470 Patent discloses diluting its docetaxel stock solutions to form perfusions: (JTX 09; '470 Patent at col. 10, ll. 9-11.) "So just dilution by a factor of two brings you from two mgs per ml to one mg per ml." (Tr. 1202:21-1203:13 (Williams)).	**Not disputed:** (JTX 16; Tarr at p. 32.)	**Not disputed:** (JTX 15; Rowinsky at p. 1251.)	Perfusions containing less than 1 mg/ml were disclosed in prior art as admitted in '561 patent itself: (JTX 03; '561 Patent at col. 1, ll. 46-55.) "[T]he prior art already taught perfusions with concentrations around one mg per ml, and that's even cited in the patent itself, from the taxol experience." (Tr. 1201:3-18 (Williams)).
"and which contains less than 35 ml/l of ethanol…"	'470 Patent discloses less than 35 ml/l of ethanol: "Just by doing the two milligram per milliliter concentration of the second stock solution, just diluting it by twofold, that brings you down two and a half percent. So you are under the three and a half percent." (Tr. 1212:19-22 (Williams)).	Tarr discloses less than 35 ml/l of ethanol: "So if you take the 30 percent stock, 30 percent ethanol stock, and dilute that by a factor of 25, you wind up with 12 ml's per liter, which is under the 35 millions per liter." (Tr. 1218:11-14 (Williams)).	**Not disputed:** (JTX 15; Rowinsky at p. 1251.)	Obvious to obtain less than 35 ml/l of ethanol starting from 50% ethanol in the GV stock solution: "Well, as we've just been doing these dilutions calculations, all you have to do is pour it into the appropriate volume. You have the perfusion in the concentration range." (Tr. 1224:17-20 (Williams)).
"and less than 35 ml/l of polysorbate,…"	'470 Patent does not use any polysorbate: "Well, zero is less than 35 milliliters per liter. So when you have zero, that would meet that limitation of less than 35 milliliters per liter." (Tr. 1213:12-14 (Williams)).	Tarr discloses less than 35 ml/l of polysorbate: "So that stock solution they were using contained ten percent polysorbate 80. Again, doing the same 25-fold dilution rate of 4 milligrams per liter, which is obviously less than 35." (Tr. 1218:19-22 (Williams)).	Rowinsky does not use any polysorbate: (JTX 15; Rowinsky at p. 1251) "[T]he paclitaxel formulation contains zero polysorbate and zero is less than 35 mls per liter." (Tr. 1223:8-9 (Williams)).	Obvious to obtain less than 35 ml/l of polysorbate starting from 50% polysorbate 80 in the GV stock solution: "Well, as we've just been doing these dilutions calculations, all you have to do is pour it into the appropriate volume. You have the perfusion in the concentration range." (Tr. 1224:17-20 (Williams)).
"capable of being injected without anaphylactic or alcohol intoxication manifestations"	See same element, claims 2 and 10.	See same element, claims 2 and 10.	See same element, claims 2 and 10.	See same element, claims 2 and 10.